Healthcare resource utilization among patients with relapsed multiple myeloma in the UK, France, and Italy

Sebastian Gonzalez-McQuire[a], Kwee Yong[b], Henri Leleu[c], Francesco S. Mennini[d], Alain Flinois[e], Carlotta Gazzola[e], Paul Schoen[a], Marco Campioni[a], Lucy DeCosta[f] and Leah Fink[e]

[a]Amgen (Europe) GmbH, Zug, Switzerland; [b]Department of Haematology, University College London, UK; [c]Public Health Expertise, Paris, France; [d]Faculty of Economics, Economic Evaluation and HTA (EEHTA), Centre for Economic and International Studies *(*CEIS), University of Rome Tor Vergata, Rome, Italy and Institute for Leadership and Management in Health, Kingston University, Surrey UK; [e]Kantar Health, Paris, France; [f]Amgen Ltd, Uxbridge, UK

Corresponding author

Sebastian Gonzalez-McQuire, Amgen (Europe) GmbH, Dammstrasse 23, 6300 Zug, Switzerland

Email: sebgonza@amgen.com

Telephone: + 41(0) 41 369 0357

Fax: +41 41 369 0400

Author contact details: *Sebastian Gonzalez-McQuire*, Dammstrasse 23, 6300 Zug, Switzerland. Telephone: +41 41 3690 357. Email: sebgonza@amgen.com; *Kwee Yong*, Department of Haematology, University College London, Gower St, Kings Cross, London WC1E 6BT, UK. Telephone: +44 20 3447 8028. Email: kwee.yong@ucl.ac.uk; *Henri Leleu,* Public Health Expertise, 157 Rue du Faubourg Saint-Antoine, 75011 Paris, France. Telephone: +33 18 5090 949. Email:

henri.leleu@ph-expertise.com; *Francesco S. Mennini,* Faculty of Economics, Economic Evaluation and HTA (EEHTA), Centre for Economic and International Studies (CEIS), University of Rome Tor Vergata, Via Columbia 2, 00198 Rome, Italy and Institute for Leadership and Management in Health, Kingston University, Kingston Hill Campus, Kingston Hill, Kingston upon Thames, Surrey, KT2 7LB, UK. Telephone: +39 06 7259 5642. Email: f.mennini@uniroma2.it; *Alain Flinois,* Kantar Health, 3 Avenue Pierre Masse, 75014 Paris, France. Telephone: +33 1 4092 6666. Email: Alain.Flinois@Kantarhealth.com; *Carlotta Gazzola*, Kantar Health, 3 Avenue Pierre Masse, 75014 Paris, France. Telephone: +33 1 4092 6666. Email: Carlotta.Gazzola@kantarhealth.com; *Paul Schoen*, Amgen (Europe) GmbH, Dammstrasse 23, 6300 Zug, Switzerland. Telephone: +41 (0) 41 3690 498. Email: pschoen@amgen.com; *Marco Campioni,* Amgen (Europe) GmbH, Dammstrasse 23, 6300 Zug, Switzerland. Telephone: +41 41 3690 300. Email: campioni@amgen.com; *Lucy DeCosta*, 1 Uxbridge Business Park, Sanderson Road. Uxbridge, UB8 1DH, UK. Telephone: +44 1895 525 000. Email: luwright@amgen.com; *Leah Fink*, Kantar Health, 3 Avenue Pierre Masse, 75014 Paris, France. Telephone: +33 14 0923 396. Email: Leah.Fink@kantarhealth.com.

Abstract

Aims: To assess the real-world healthcare resource utilization (HRU) and costs associated with different treatment regimens used in the management of patients with relapsed multiple myeloma in the UK, France, and Italy.

Methods: Retrospective medical chart review of characteristics, time to progression, level of response, HRU during treatment, and adverse events (AEs). Data collection started on 1 June 2015 and was completed on 15 July 2015. In the 3 months before record abstraction, eligible patients had either disease progression after receiving one of their country's most commonly prescribed regimens or had received best supportive care and died. Costs were calculated based on HRU and country-specific diagnosis-related group and/or unit reference costs, amongst other standard resources.

Results: Physicians provided data for 1282 patients (387 in the UK, 502 in France, 393 in Italy) who met the inclusion criteria. Mean [median] total healthcare costs associated with a single line of treatment were €51 717 [35 951] in the UK, €37 009 [32 538] for France, and €34 496 [42 342] for Italy, driven largely by anti-myeloma medications costs (contributing 95.0%, 90.0%, and 94.2% of total cost, respectively). During active treatment, the highest costs were associated with lenalidomide- and pomalidomide-based regimens. Mean cost per month was lowest for patients achieving a very good partial response or better. Unscheduled events (i.e. not considered part of routine management, whether or not related to multiple myeloma, such as unscheduled hospitalization, AEs, fractures) accounted for 1–9% of total costs and were highest for bendamustine.

Limitations: The use of retrospective data means that clinical practice (e.g. use of medical procedures, evaluation of treatment response) is not standardized across participating countries/centers, and some data (e.g. low-grade AEs) may be incomplete or differently adjudicated/reported. The centers involved may not be fully representative of national practice.

Conclusions: Drug costs are the main contributor to total HRU costs associated with multiple myeloma. The duration of active treatment may influence the average total costs, as well as response, associated with a single line of therapy. Improved treatment outcomes, and reductions in unscheduled events and concomitant medication use may therefore reduce the overall HRU and related costs of care in multiple myeloma.

Short title: Costs and resource use in relapsed multiple myeloma

Introduction

Multiple myeloma is one of the more common hematological malignancies, with an incidence of 4.5–6.0 per 100 000 people per year in Europe, and accounts for approximately 1% of all cancers [1,2]. Although the age range of patients with multiple myeloma is broad (28–91 years), most patients are elderly (median age at diagnosis is 60–71 years) [3] and the incidence can be expected to rise as the population ages. Several new therapies have become available for multiple myeloma in recent decades and have altered the disease course, to the extent that patients are now surviving for longer than ever before [4,5]. Comparisons of patients diagnosed with multiple myeloma since 2000 and those diagnosed before 2000 show that median overall survival has improved by 50% (44.8 vs 29.9 months; $p < 0.001$), with similar improvements observed for relapsed/refractory multiple myeloma (30.9 vs 14.8 months; $p < 0.001$) [4]. These findings suggest that healthcare resource utilization (HRU) and costs associated with the treatment of patients with multiple myeloma will increase as outcomes improve, because patients will be treated for longer [6]. This is particularly pertinent given that the toxicity profiles of the newer anti-myeloma agents make maintenance therapy (i.e. continuous therapy to maintain long-term disease control following initial disease reduction and consolidation therapy) more feasible [7].

Several large studies examining the real-world costs of multiple myeloma in the USA and China have been published in the last few years [6,8,9] but recent European data (since 2013) reporting costs associated with novel agents are lacking. In particular, the relatively recent availability of pomalidomide and bendamustine has not been captured in the few published European studies [10-14]. Furthermore, the studies were small, were conducted in single countries, studied only elderly patients, considered only costs associated with first-line treatments, and

estimated variables based on results from clinical studies rather than collecting real-world data [10-14]. In addition, there is a lack of information on real-world HRU and costs associated with disease management and outcomes in multiple myeloma, best supportive care (BSC) at end of life, non-treatment-related costs, and cost drivers.

Robust European data are required that include not only treatment costs and costs associated with adverse events (AEs) but also HRU associated with real-world factors that may not be captured in clinical trials and by prediction of costs. To gain a complete picture of the disease course in patients with relapsed multiple myeloma, data must be collected during active treatment, during periods when patients are off treatment and before further disease progression (i.e. in remission or with stable disease), and after progression. Data collection should also encompass both planned HRU (anti-myeloma drugs and administration, concomitant medications, consultations, planned hospitalizations, laboratory tests, radiotherapy, scans, and other procedures) and unscheduled HRU (any event that requires the use of medical resources that is not considered usual management, such as unexpected hospitalization). Accordingly, this study aimed to assess the real-world HRU and costs associated with different treatment regimens used in the care of patients with relapsed multiple myeloma in the UK, France, and Italy, including all relevant treatment periods from second line (2L) treatment onwards.

Methods

Study design and ethical conduct

This was a real-world, non-interventional, observational study that collected retrospective medical record data from electronic case report forms (eCRFs). In the

UK, Health Research Authority approvals are only required when the National Health Service (NHS) has a duty of care to participants in relation to the research activity, either as service users or NHS staff or volunteers, or when the resource required for the study (i.e. data or human biological material) are under the responsibility of the NHS organization as a healthcare provider. In our study, we recruited physicians directly through Epidemiologic Research Assistance (ERAs) and not through their hospital. Therefore, approval was not required because physicians were responding as individuals; we did not use NHS resources [15]. In France, this study is classified as Type 3 research / Art. L1121-1 3° CSP (non-interventional research) type B (research with data only). This type of study is not required to be submitted to the Comité de Protection des Personnes (CPP) and prior to 2017 was not subject to further submissions, owing to the retrospective and anonymous nature of the data collection. Kantar Health also had an authorization from the Commission Nationale de l'Informatique et des Libertés (CNIL; number 1493177) to conduct these studies. Since the time this study was conducted, the regulations have changed and now require that a letter of information be submitted to the Comité consultatif sur le traitement de l'information en matière de recherche and in certain situations, an additional submission to the CNIL and the Conseil National de l'Ordre des Médecins. In Italy, all ethics approvals are site based as there is no centralized Ethics Committee. As this study was not conducted through sites but by contacting specific physicians meeting inclusion criteria, no ethics approval was required [16].

As this was a retrospective study using de-identified patient data, approval by an ethics committee was not required. The study was conducted in accordance with legal and regulatory requirements, and followed the accepted research practices described in the Good Epidemiological Practice guidelines issued by the

International Epidemiological Association [17]. All data were handled in strictest confidence and we conformed with national and European data protection regulations, such as Directive 95/46/EC. Anonymity of the data was maintained. Each patient was assigned a study specific identification number that cannot be traced back to any specific patient. There is no information held by Kantar Health or Amgen that can be used to identify any patients.

Objectives

The primary objectives were: 1) to quantify HRU and costs associated with managing patients with relapsed multiple myeloma, from initiation of 2L treatment, reflecting the most commonly used regimens for treatment line in each country [18,19], and 2) to determine the major drivers of healthcare costs within and across these treatment lines. Secondary objectives included distinguishing between HRU and associated costs that were planned (i.e. expected within routine treatment practice, including planned hospitalizations) and unscheduled (such as AEs, hospitalizations, and other unexpected events requiring medical resources that were not considered in normal monitoring or treatment). HRU and associated costs were also analyzed according to each treatment line, drug regimen, and level of clinical response, and in specific time periods defined by the main treatment regimen.

Inclusion criteria

Stratified sampling was used to select representative physicians (those typically involved in the management of patients with relapsed multiple myeloma) in terms of region and hospital type. Eligible physicians had to be personally responsible for the initiation of treatment in patients with symptomatic multiple myeloma, to manage at least 15 patients with symptomatic multiple myeloma each month, and to have at

least 3 years' clinical experience.

Eligible patients were adults (aged > 18 years at treatment initiation) with symptomatic multiple myeloma who, in the 3 months prior to the study start, had received one of the pre-specified multiple myeloma treatment regimens (from 2L onwards), had disease progression after treatment, or had received BSC and died.

To narrow the scope, complexity, and cost of the study whilst maintaining the real-world relevance, the treatment regimens to be included in the study (listed in Table 1) were selected based on the real-world treatment patterns identified in a 2014 European observational chart review [18]. These regimens were selected on the basis of the frequency of use in each country; these data were considered to represent current real-world treatment patterns and to reflect more than three-quarters of 2L and 3L prescribing practice within the participating countries [18]. The treatment regimens in the UK also reflected recommendations by the National Institute for Health and Care Excellence (NICE) [20-22]. Combinations of the pre-specified treatment regimens with other agents, such as dexamethasone or cyclophosphamide, were permitted (Supplementary Table 1). If a patient received more than one agent of interest, physicians decided which of the pre-specified treatment regimens they would be allocated to.

Data collection

Data were collected between 1 June and 15 July 2015. Physicians from enrolled centers were provided with the list of the most commonly prescribed anti-myeloma drug regimens in their country, as described above, and were asked to indicate those for which they had a corresponding patient. Each physician provided eCRFs for up to 11 patients, one for each of the specified regimens listed; physicians with

more than 11 relevant patients completed the 11 eCRFs according to the least commonly prescribed regimens for that particular country, whilst those with fewer than 11 eligible patients completed eCRFs as their caseload permitted.

The eCRFs for each patient captured retrospective data on patient characteristics (with baseline defined as the time of initiation of drug therapy), disease progression, level of response, HRU (anti-myeloma drugs and administration [including dose and location of treatment], concomitant medications, consultations, planned hospitalizations, laboratory tests, radiotherapy, scans, and other procedures) and unscheduled events (defined as healthcare contacts associated with multiple myeloma [e.g. disease- or treatment-related complications], or not, that required the use of medical resources not part of routine care [e.g. unscheduled hospitalization, AEs, and fractures]).

The eCRFs were designed to ensure that all resources were accounted for only once and were accurately attributed to the corresponding regimen, line of therapy, and time period in the patient journey. Patient quotas were predefined for each therapy line to ensure sufficient sample sizes in later lines (Supplementary Table 2); patient cases were selected in reverse chronological order until quotas were met. Data collection was restricted to the period between the beginning of the last completed therapy line (any of 2L to 5L+) until the start of the next treatment line or death. Patients were not followed longitudinally across multiple lines of treatment. This approach ensured that the data collected were relevant to the current real-world situation.

As shown in Figure 1, “a line of therapy” could consist of up to three periods: (i) active treatment; (ii) off-treatment (in remission or with stable disease), and (iii) post-

progression. A single therapy line was defined as the period between starting a specific anti-myeloma drug regimen and starting the subsequent regimen following disease progression. Dose changes were not considered to be a new therapy line, and retreatment with the same regimen was only considered to be a new line if it followed disease progression. *Active treatment* was defined as the period during which a patient was treated with a specific anti-myeloma drug regimen until they discontinued therapy because of an AE or relapse, or came to the end of a pre-specified number of treatment cycles. The *off-treatment period* encompassed periods of disease remission and stable disease, during which patients did not receive anti-myeloma treatment; this period continued until disease progression. *Post-progression* was defined as the period between relapse and the start of the next anti-myeloma drug regimen. The *time to progression/pre-progression period* was defined as the time from the start date of active treatment until the date of progression (active treatment period plus off-treatment period).

Post-progression data were collated from the eCRFs for patients who initiated a new line of therapy following progression; data from patients who died post-progression but before initiation of the next line were not included. This approach avoided any distortion of data that may have resulted from the inclusion of patients in a treatment line who did not progress to a subsequent line. These post-progression data were collated from the eCRFs for patients on the subsequent line of therapy. Therefore, the post-progression population within each line comprised different patients from those who contributed data to the active treatment plus off-treatment period. For example, to capture resource use following progression on a 2L treatment and the initiation of a 3L treatment, the eCRFs for patients who completed a 3L treatment were used, wherein physicians documented the details of the

previous 2L treatment; this allowed resource use between the end of 2L and initiation of 3L to be accurately attributed to a 2L treatment regimen. Although a limitation of the study design and potential source of bias, as the pre- and post-progression data were collected from the same study centers and under the same methodologies, any resultant bias should be limited.

Cost and healthcare resource utilization analyses

Costs were calculated based on HRU and country-specific diagnosis-related group and/or unit reference costs, with the following resources used to estimate the costs for drugs and additional resources, such as hospitalizations and laboratory tests (details shown in Supplementary Tables 2 and 3).

(i) For the UK, specific costs were obtained from the Department of Health [23], the University of Birmingham [24] and the online resource 'MedicinesComplete' [25]. Costs of other drugs and resources (e.g. hospitalization and laboratory tests) were estimated from standardized schedules [23]. To enable comparison between countries, the exchange rate at the study start date (1 June 2015) was used to convert pounds to euros (£1 = €1.3931).

(ii) For France, drug and ambulatory costs (e.g. consultations and laboratory tests) were estimated using the national health insurance tariffs [26-29].Hospital costs were obtained from the National Hospital Costing Study (Echelle Nationale des Coûts) [30].

(iii) For Italy, specific costs were calculated using information from Codifa, the Italian database of health products and drugs [31] the Italian Drug Agency (AIFA)

[32], the Italian Ministry of Health [33,34], tariff prices for the region of Veneto [35] and from healthcare costs published within the medical literature [36-39]. Costs of other drugs and resources were estimated based on standardized schedules such as those outlined by Oncomip [40].

Total costs were defined as the sum of the costs associated with the following healthcare resources: anti-myeloma drug treatment, other concomitant medications, hospitalizations, outpatient consultations, laboratory tests, monitoring procedures, scans, radiotherapy, and other procedures. Costs of anti-myeloma treatments accounted for the number of cycles, the number of days of drug administration per cycle, the dose, the price and volume per unit of each treatment (Supplementary Table 2), and the weight/body surface area of the patient. Outpatient administration costs were also added for drugs that had to be administered intravenously or subcutaneously. Costs for other concomitant medications were based on the number of administrations, the mean dose per administration, a reference dose, and the price per unit. Hospitalization costs and costs associated with all other clinical testing, monitoring, scans, and procedures were calculated from country-specific tariffs (Supplementary Tables 2 and 3).

Treatment duration and costs were also analyzed across all countries according to the level of therapeutic response. Definitions and criteria were based on the Eastern Cooperative Oncology Group (ECOG) performance status (PS) scoring and the physician-assessed International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma [41] categories of very good partial response or better (VGPR+), partial response (PR), stable disease (SD), or progressive disease (PD).

Data analyses

Data analyses were presented using descriptive methods. The study was not designed to test for differences between samples, and the relatively small sample sizes and typical skewness of data relating to the costs and durations of treatments limited the applicability of standard parametric statistical tests. Categorical data were summarized by the number and percentage of patients. Continuous data were summarized by mean and standard deviation (SD) or standard error, as well as median and, where relevant, minimum and maximum values.

Results

Study participants

A total of 189 physicians in the UK (n = 56), France (n = 76), and Italy (n = 57) participated in the study, providing data from 387, 502, and 393 patients, respectively (1282 patients in total). Physician characteristics are described in Supplementary Table 4; the majority were hematologists (71%, 61%, and 91%, respectively).

The baseline demographics and disease characteristics of patients (Table 1), as well as the response to treatment (Table 2), and the duration of each treatment period (Table 3), were evaluated by country and according to each therapy line and treatment. Baseline demographics (including country-specific subpopulations) were consistent with those expected from a ‘typical’ population of patients with relapsing or remitting multiple myeloma, including: a greater proportion of men than women; a mean age of more than 60 years; and some degree of renal impairment in more than half of patients at the time of initiating 2L (Table 1) [3]. Although patients were

reasonably well distributed across treatment lines within each country, population demographics differed in the three countries. Patients in the UK tended to be younger at diagnosis and at initiation of earlier treatment lines than those in France and Italy but this age difference was less apparent in later treatment lines. Patients in France were older, with a longer interval between diagnosis and initiation of 2L treatment. Patients in Italy tended to have been diagnosed at earlier disease stages (i.e. International Staging System stages I and II) than patients in the UK and France, but also had a higher proportion presenting with an ECOG PS score of at least 2. The proportion of patients with an ECOG PS score of 0 or 1 at initiation of a treatment line was highest in the UK, and for all three countries, the proportion of patients with an ECOG PS score of 2 or less increased from 2L to 5L treatment. Fewer patients had received a stem cell transplant (SCT) in the UK than in France and Italy.

Treatment duration and cost in the pre-specified treatment lines according to treatment periods

The mean and median durations of the treatment periods (active treatment, off-treatment, post-progression; Table 3) and the associated costs (Table 4), according to treatment line and the pre-specified treatments within those lines, were evaluated.

The mean duration of active treatment across all treatment lines (average over treatment-stratified sample) was 7.4 months in the UK, 8.8 months in France, and 8.7 months in Italy (medians were 6, 7, and 6 months, respectively). The mean time to progression (active treatment + off-treatment period until the start of the next treatment line) was 10.9, 12.5, and 14.7 months, respectively (medians were 6, 8,

and 8 months, respectively). For patients receiving anti-myeloma drug treatments, lenalidomide-based regimens were associated with the longest duration of treatment in all three countries, and were generally longer in France and Italy than in the UK.

The mean (SD)/median total cost per single therapy line (average over treatment-stratified sample) was €51 717 (42 342)/€35 951 in the UK, €37 009 (31 530)/€32 538 in France, and €34 496 (40 305)/€23 770 in Italy, with 95.0%, 90.0%, and 94.2% of these costs attributable to anti-myeloma drugs. Irrespective of therapy line and country, the total mean costs were consistently higher for lenalidomide- (€42 584–70 260) and pomalidomide-based regimens (€64 468–78 595) across the 2L–5L+ treatment lines and were lowest for bendamustine-based regimens (€8454–18 846) (Table 4). A similar trend was seen for median costs (Supplementary Table 5). The costs per line and treatment during the active treatment period with each agent did not vary greatly across treatment lines because the durations of therapy were similar. To account for the potential contribution of longer active treatment periods to increased costs, the mean total costs were adjusted accordingly and presented as mean monthly costs (Table 4). The differences in costs between lenalidomide and bortezomib were less apparent once treatment duration was accounted for.

There was some variation in costs across countries: the 2L lenalidomide-based regimen in Italy was approximately 20% more expensive than in the UK and 36% more expensive than in France.

Treatment durations and costs in each therapy line according to level of response

The duration of the treatment periods (active treatment, off-treatment, post-progression) and the associated costs were evaluated according to the levels of

patient response within each therapy line. As shown in Table 2, the treatment lines associated with the greatest proportions of patients achieving a VGPR+ were 2L bortezomib (UK, 54%; Italy, 50%) and 3L lenalidomide (France, 56%), with a considerable proportion of patients achieving a complete response (CR) on 2L and 3L treatments (4–11% in the UK; 3–16% in France; 8–14% in Italy). For all countries, the rates of SD + PD tended to increase with treatment line.

The mean time to progression (i.e. from initiation of treatment to progression) was analyzed for all patients and lines (average over treatment-stratified sample) according to the level of response. Patients who had achieved a VGPR+ had also spent the longest time on active treatment (9.7, 11.4, and 11.5 months in the UK, France, and Italy, respectively); this was longer than in the total study population for each country (7.4–8.8 months) (Figure 2). In all countries, the mean time to progression was shorter in the SD + PD subgroup than in the overall study population, as were the active treatment and off-treatment periods (Figure 2).

Because of the longer treatment duration (active treatment period) in patients achieving a VGPR+, the total mean costs from treatment initiation to progression (i.e. during the active treatment and off-treatment periods) were higher in these patients than in the overall study population, especially compared with those who achieved SD + PD, for whom total mean costs during the same period were lower than in the overall study population (Figure 3).

To account for the potential influence of longer active treatment periods on increased costs, the mean total costs were adjusted accordingly and presented as mean monthly costs (Figure 4).

Costs according to ECOG PS and SCT status

Across all countries, the mean and median costs during the active treatment period tended to decrease with worsening PS, likely the result of shorter treatment duration in patients with more advanced disease. Patterns during the other periods were less clear, with off-treatment and post-progression costs decreasing with worsening PS in the UK whereas costs tended to be highest in patients with an ECOG PS score of 2 or higher in France and Italy (Supplementary Table 6).

In France and Italy, the mean and median costs during active treatment were lower in patients who did not receive an SCT than in those who did, perhaps indicating different treatment patterns in these subpopulations. In the UK, however, costs were similar in patients who did and did not receive an SCT. There were no clear trends in costs during the off-treatment period. In the UK, these costs were lower in patients who did not receive an SCT than in those who did, whereas no strong trends were seen in the other two countries (Supplementary Table 7).

Distribution of non-anti-myeloma treatment-related costs by treatment period

Approximately 90% of the costs evaluated in this study were attributable to anti-myeloma drugs, with the remaining costs distributed over other resources, including concomitant medications, hospitalizations, outpatient consultations, laboratory tests, radiography, scans, and other procedures (Table 4, Figure 5). The contribution of anti-myeloma drugs to overall cost was consistently close to 90% across treatment lines although in France and Italy, it was slightly lower at 5L+ than at other lines, and with bendamustine compared with the other drugs. After excluding the costs of anti-myeloma drugs and AE management, 38% of the non-treatment-related costs in the

UK and 40% in France were attributable to concomitant medications, compared with 29% in Italy (Figure 5). These proportions generally remained similar across the off-treatment and post-progression periods in France and Italy but were approximately halved in the UK.

As shown in Figure 5, across all countries and treatment segments, approximately one-third of non-anti-myeloma treatment-related costs resulted from laboratory tests, with hospitalizations also accounting for a large proportion across the three treatment periods (23–48% in the UK; 16–25% in France; 20–33% in Italy). For all countries, the highest proportion of hospitalizations occurred during the off-treatment period (Figure 5). During the active treatment period, the proportion of non-anti-myeloma drug costs was generally highest in France, across all HRU types, treatment lines, and regimens, with the exception of 'radiography, scans, and other procedures', for which costs were highest overall in Italy (Table 4). By contrast, costs associated with outpatient consultations were lowest in the UK, ranging from €22 to €39, compared with €137–250 for France, and €69–216 for Italy (Table 4).

Hospitalizations by treatment period and patient response

In general, the proportion of patients requiring at least one hospitalization increased with successive treatment lines (2L–5L+) in the UK (10–22%) and France (17–26%), but there was no obvious trend in Italy (15–24%) (Table 5, Figure 6). Across all treatment lines (2L–5L+) and countries, 16–18% of patients experienced one hospitalization and 3–6% of individuals experienced two or more.

Although the proportion of costs associated with hospitalizations in each country was highest in the off-treatment period (Figure 5), the largest proportion of hospitalizations occurred during the active treatment period (Figure 7). The main reasons for

hospitalizations among patients on active treatment were drug administration (28–53% of hospitalizations), palliative care (32–41%), and management of AEs (14–41%).

The highest proportion of hospitalizations during the active treatment period occurred in the 5L+ period for France (73%) whereas the highest proportions in the UK and Italy were for 2L treatment (78% and 58%, respectively). Hospitalization were generally more common in the UK, with 71% of patients receiving active treatment in 3L, and 67% in 4L requiring at least one hospitalization (Figure 7).

The highest mean [SD] number of hospitalizations occurred during 2L in the UK (1.8 [1.1]), in 4L in France (1.7 [1.6]), and in 2L (1.2 [0.9]) and 3L (1.2 [0.6]) in Italy. In the UK and France, the mean (SD) length of hospital stay tended to increase with each therapy line, from 7.2 (4.6) and 5.7 (5.8) days, respectively, with 2L therapies compared with 8.1 (4.5) and 9.6 (9.4) days, respectively, with 5L+. The opposite was true in Italy, however, where the mean (SD) duration of hospital stay with 2L, 3L, 4L, and 5L+ was 9.7 (7.0), 5.0 (5.6), 4.2 (4.9), and 4.5 (6.5) days, respectively.

In all countries, the proportion of patients requiring hospitalization was lower among those who achieved VGPR+, and higher among those with SD + PD, compared with the overall study population. Of the patients who achieved VGPR+, 11–16% were hospitalized whereas this proportion was almost doubled for patients with SD + PD (27–28%).

Costs of planned and unscheduled resource use

The cost of unscheduled events (i.e. AEs, unscheduled hospitalizations, and other unexpected events not considered part of normal monitoring or treatment) was

≤ 1% of the cost of treatment in UK; in France, the proportion was ≤ 2% for all 2L, 3L, and 4L therapies except for 3L and 4L bendamustine-based regimens, where the low costs of treatment raised the proportional costs of unscheduled events to 9%. In France, unscheduled events were equal to 5% of the cost of treatment at 5L+. Similar trends were observed in Italy, where the cost of unscheduled events was equivalent to 1–3% of the costs of 2L, 3L, and 4L therapies, except for bendamustine-based regimens, for which the costs of unscheduled events were equal to 3–6% of total treatment costs. Unscheduled events in 5L+ represented 4% of treatment costs in Italy.

Discussion

The results from this large European real-world study show that the management of patients with relapsed multiple myeloma in clinical practice is associated with significant HRU and costs. Patient baseline characteristics indicate that the sample had typical features of patients with relapsed and/or refractory multiple myeloma [3].

The regimens included in this analysis are representative of those used in clinical practice in Europe at the time of the study. The European chart review study found that lenalidomide-based regimens were commonly used in the second- and third-lines (59% and 51%, respectively), followed by bortezomib-based regimens (25% and 13%, respectively) and thalidomide-based regimens (7% and 4%, respectively) [18]. Pomalidomide- and bendamustine-based regimens were mainly used in later lines (4L and beyond) [18], as reflected in the regimens analyzed in our study. Despite its use in advanced therapy lines, bendamustine was associated with good real-life treatment outcomes (Table 3) and was the lowest-cost treatment

option evaluated in this study. Bendamustine is currently licensed for use in combination with prednisone in elderly patients (aged ≥ 65 years) with multiple myeloma who are not eligible for an SCT and who cannot be treated with thalidomide or bortezomib [42]; however, European consensus panels recommend its use only in relapse/remitting disease [43] and in the UK access is possible only via the Cancer Drugs Fund, for the treatment of relapsed multiple myeloma where other treatments are not appropriate [44]. The real-life outcomes associated with bendamustine-based regimens in this study may reflect a degree of indication bias within the data, with clinicians preferentially selecting a less effective but known therapy in patients with less aggressive disease.

As expected, treatment durations were longer with lenalidomide-based regimens than with bortezomib-based regimens, reflecting the different schedules outlined in the product labels. Lenalidomide can be administered until disease progression or intolerance [45], whereas bortezomib should be given for a set number of treatment cycles (one 3-week cycle initially; two cycles following a CR; eight cycles in responding patients who do not achieve CR) [46]. In patients who have received one or more previous therapies, lenalidomide should be continued or the dose modified according to clinical and laboratory findings, unless toxicity is unmanageable or disease progression occurs [45], which suggests that there should be no off-treatment period in the absence of toxicity. We noted, however, long off-treatment periods with this agent: 2.5–4.9 months in the UK, 2.2–4.2 months in France, and 4.3–4.9 months in Italy, suggesting that not all patients were treated until disease progression. Similar findings were reported in another real-world analysis of treatment patterns in patients with multiple myeloma, in which only 22% of patients receiving 2L lenalidomide were treated until disease progression [19]. Physicians may choose to end treatment early because of the association between longer treatment-free intervals and better quality of life [47]. Alternatively, a previous

observational study indicated that, in the 18% of patients for whom lenalidomide was discontinued early, three-fifths ended treatment because they had SD and two-fifths discontinued because of toxicity [48].

Total costs of management were substantial and were driven largely by the costs of anti-myeloma drug treatment; lenalidomide-based regimens were the main cost driver in all three countries. This is in line with results from single-country European studies, which have reported high costs of multiple myeloma treatment, driven mainly by the costs of anti-myeloma drugs (particularly the new agents) and hospitalization/management of AEs [10-12,14]. Total costs differed substantially across the three countries, likely reflecting country-specific differences in treatment regimens, durations, and costs.

Although treatment durations for given regimens were broadly similar across treatment lines, costs tended to increase with line. This was probably due to the high cost of pomalidomide, which is used only in later lines. Similarly, increasing costs with treatment line have been observed in an analysis of Dutch registry data from patients with relapsed and/or refractory multiple myeloma [12]. The increase in healthcare costs in later lines was attributed to worsened prognosis and greater need for hospitalization [12]. By contrast, data from other studies show that costs tend to be highest during earlier lines of treatment and decrease at later lines, likely because of shorter durations of treatment [49,50]. In our study we observed some country-specific differences in how different agents were used. For example, lenalidomide is usually given until disease progression whereas bortezomib is usually given for a set number of cycles. We did, however, identify patients who had received bortezomib for longer than the stipulated eight cycles. It should also be

noted that in the UK, four cycles are recommended initially and patients receive further cycles only if they achieve a PR; however, this guidance does not apply in France or Italy. Accordingly, we observed that French and Italian patients received bortezomib for slightly longer than do UK patients (data not shown). Additionally, the relatively long off-treatment period for lenalidomide in particular (noted above) suggests that patients were not treated until disease progression, which may explain why typical trends between treatment line and total costs were not detected.

Given the differences in the length of treatment regimens specified in the product label (some agents are given for a fixed number of cycles whereas others are given until progression or can be used as maintenance therapy), monthly costs may be a more appropriate method for comparing costs across treatment types. Mean monthly costs peaked at 4L in both the UK and France but decreased with treatment line in Italy. Pomalidomide was associated with the highest mean monthly costs in France and the UK. Data were not available for pomalidomide in Italy, and lenalidomide demonstrated the highest monthly costs. For all three countries, costs per month on treatment were in line with those reported for bortezomib and lenalidomide in another real-world study, in which mean monthly costs for these agents across 2L–4L ranged from €4215 to €6260 [12], compared with €3742–7159 in our study. Unsurprisingly, 2L pomalidomide and 4L lenalidomide were the most expensive treatments. Most costs were attributable to drug costs; the remainder were attributable to concomitant medication, laboratory tests (which may have included tests to ascertain response status), and hospitalizations.

Unscheduled events (e.g. AEs and unscheduled hospitalizations) were uncommon in all countries. Because patients with relapsed disease are relatively

well managed and monitored, unscheduled events are largely addressed in the clinic. However, the proportions of unscheduled costs tended to increase with treatment line in all countries and were proportionally highest for bendamustine, probably because its low cost means that any non-treatment costs are disproportionately large.

Most unscheduled hospitalizations occurred during the active treatment period, most likely for AEs. However, there are limitations in gathering real-world hospitalization and AE data (see study limitations) necessitating caution when making inferences from this finding. Importantly, the proportion of patients hospitalized was lower among those achieving VGPR+ than for those with SD + PD. This shows that improving the depth of response may improve resource use and the patient experience, in addition to the primary objective of increasing survival. The mean length of hospital stay for patients receiving 2L treatment was longer in Italy than in the UK or France, although this may reflect the higher proportion of patients who underwent SCT at 2L in Italy (28–36%, vs 10–17% in the UK and 20–22% in France).

Mean total costs were higher for patients who achieved VGPR+ than for the overall population, because of the longer duration of treatment, whereas mean monthly costs were generally lower than for the overall population, even when treatment costs were excluded. Thus, although VGPR+ responses are likely to be associated with higher total costs because patients are treated for longer before disease progression, the cost–benefit ratio is likely to be beneficial overall as a result of the significantly lower monthly costs and fewer hospitalizations.

Many studies have estimated costs based solely on approved dosages or AE rates reported in clinical studies, and do not take into account real-world HRU resulting from unscheduled events such as hospitalizations or specialist visits. In addition, dosing and drug administration can differ substantially between real-world practice and clinical trials, because the patients encountered in clinical practice tend to have more heterogeneous disease characteristics and are generally in poorer health than the carefully selected patients involved in clinical trials, who must meet strict inclusion criteria [13]. Real-world dosages and drug combinations may also differ markedly from approved treatment regimens and those used in clinical trials, because in the real-world setting physicians have greater flexibility to adjust treatment according to patients' preferences and to reduce AEs and improve quality of life. Cessation of treatment in practice – because of insufficient clinical response or tolerability issues – also affects real-world costs in a manner that is not reflected by clinical trials.

Another limitation of using clinical trial data to estimate costs and outcomes is that only drug-related AEs are reported, and other relevant disease-related events are not considered (especially in patients with progressive disease, who might have been excluded from clinical trials). In addition, costs associated with natural disease progression, including during the off-treatment period (in remission or with SD), are unlikely to be captured, neither are costs associated with hospitalizations and non-treatment-related factors. Likewise, assumptions about average treatment costs cannot accurately predict real-world costs because of the wide variation in HRU associated with disease management. Thus, an assumptions-based average-cost approach can yield inaccurate cost predictions associated with large uncertainties.

Study limitations

The current study has a number of limitations. While the regimen- and country-specific data are reliable estimates, costs were not weighted to account for country-specific differences in treatment types, diagnostic tests, or supportive care, for example. Thus, pooled data (by line or treatment) should not be used to compare equivalent costs of multiple myeloma in the countries studied. Furthermore, treatment pathways and costs differ between countries, so care should be taken when extrapolating results to other European countries. Site selection bias may also have occurred, as some small centers may not have had the capacity to participate in the study, and other centers may not have been willing. Management of patients at sites other than hospitals and cancer centers is not captured here.

The decision to exclude patients who died during active therapy from the analyses may have introduced bias resulting in potential over-estimation of actual costs. Nevertheless, this approach seems reasonable assuming that most patients who die from multiple myeloma are in the progression state rather than on treatment/or progression-free.

Moreover, although reporting durations and costs against different responses is useful for future studies, reporting response results alone may not be appropriate in this instance, mainly because the sample size of the current study is limited and this is not a trial study. Reporting response results in isolation could lead to misinterpretation of the results as treatment effects.

The pre-selection of treatment regimens may also have introduced bias towards inclusion of patients with certain profiles, and some treatment combinations may not

have been captured. In addition, the treatment regimens included were based on those identified in a real-world chart review from 2014; since then, several new therapies have become available, such as carfilzomib, elotuzumab, and daratumumab [51-53]. These agents have improved treatment responses [51-53] and would also be expected to affect resource use and costs. Furthermore, the treatment groups we defined (‘lenalidomide’, ‘bortezomib’, ‘pomalidomide’) could include several different regimens, and costs might be expected to vary considerably within these groups.

It is worth noting that, in the UK, fewer patients than expected had undergone SCT. Some bias may also have resulted from the exclusion of patients who died during active treatment. In the eCRFs, the number of routine laboratory tests was collected as a frequency (e.g. once a week) then multiplied by the period length to estimate the total number, which may have been imprecise (especially for the shorter off-treatment and post-progression periods). In addition, although definitions of unscheduled events were included in the eCRF, physicians may have had different opinions about what constitutes such an event. It is also important to reiterate that, according to the study design, the data for the post-progression period for any one treatment line were obtained from a different set of patients than the data for analysis of active treatment and off-treatment periods.

Real-world studies are inherently associated with specific limitations, such as differences in the ways that physicians evaluate patients and the strict criteria used in clinical trials. This was particularly relevant for depth of response data in the current study, because response judgments were based on each physician’s practice habits rather than on conventionally defined criteria (as is the case in clinical

trials). Thus, these results should be interpreted with caution. Although this could be perceived as a limitation, we believe that it is, in fact, a strength, as it accounts for differences that occur in real-world clinical practice, such as how long treatments are administered. However; while the treatment durations, costs, and associated response rates reported have utility for future research and study design, the sample sizes involved were limited and the real-world nature of the study design lacks the internal validity of a clinical trial. Care should be taken when interpreting and reporting the response rates, in order to avoid misinterpretation and misappropriation of treatment-associated effects. There may have been potential for bias in capturing AEs; for example, lower-grade AEs may have been managed by a nurse or primary care physician and may not have been reported, generating a proportional bias in favor of higher-grade AEs; physicians may have only been aware of AEs that occurred while the patient was hospitalized on their ward.

Future perspectives

A more detailed longitudinal study of treatment patterns and therapy lines would give more insight into the approaches used in the management and treatment of relapsed multiple myeloma.

Conclusions

This study using real-world European data found that the main drivers of direct costs associated with multiple myeloma were drugs, hospitalization, and management of AEs. Patients who achieved a VGPR+ incurred higher overall costs than those who achieved lesser responses (PR or lower) because of longer treatment duration. However, patients with a VGPR+ had lower monthly costs and fewer hospitalizations than those who responded less well to treatment, probably

reflecting better disease management and fewer unscheduled events and prescriptions for concomitant medication. This analysis of real-world use of treatment regimens for multiple myeloma highlights the importance of optimizing the management of these patients, as this has a clear impact on outcomes, HRU, and associated costs.

Transparency

Declaration of funding

This study was funded by Amgen (Europe) GmbH.

Declaration of other financial interests

SG-M, PS, MC, and LDC are employees of Amgen and hold Amgen stock.

KY has received honoraria from Amgen, Janssen-Cilag, Novartis, Celgene, and MorphoSys.

HL and FSM have received honoraria from Amgen.

AF, CG, and LF were paid by Amgen to conduct the study.

Author contributions

All authors contributed equally to the conception, design, and interpretation of the data and subsequent manuscript preparation. All authors agree to be accountable for all aspects of the work.

Acknowledgments

Medical writing support was provided by Kim Allcott PhD and Liz Hartfield PhD of Oxford PharmaGenesis Ltd, and was funded by Amgen (Europe) GmbH.

Previous presentations

Part of these analyses were presented at the International Society for Pharmacoeconomics and Outcomes Research 21st Annual Meeting, May 21–25 2016, Washington, DC, USA and at the European Hematology Association 21st Annual Meeting, 9–12 June 2016, Copenhagen, Denmark.

References

[1] Kariyawasan CC, Hughes DA, Jayatillake MM, Mehta AB. Multiple myeloma: causes and consequences of delay in diagnosis. QJM 2007;100:635–40.
[2] Moreau P, San Miguel J, Ludwig H, Schouten H, Mohty M, Dimopoulos M, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi133–7.
[3] Dimopoulos MA, Terpos E, Niesvizky R, Palumbo A. Clinical characteristics of patients with relapsed multiple myeloma. Cancer Treat Rev 2015;41:827–35.
[4] Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516–20.
[5] Ludwig H, Sonneveld P, Davies F, Blade J, Boccadoro M, Cavo M, et al. European perspective on multiple myeloma treatment strategies in 2014. Oncologist 2014;19:829–44.
[6] Roy A, Kish JK, Bloudek L, Siegel DS, Jagannath S, Globe D, et al. Estimating the costs of therapy in patients with relapsed and/or refractory multiple myeloma: a model framework. Am Health Drug Benefits 2015;8:204–15.
[7] Lipe B, Vukas R, Mikhael J. The role of maintenance therapy in multiple myeloma. Blood Cancer J 2016;6:e485.
[8] Arikian SR, Milentijevic D, Binder G, Gibson CJ, Hu XH, Nagarwala Y, et al. Patterns of total cost and economic consequences of progression for patients with newly diagnosed multiple myeloma. Curr Med Res Opin 2015;31:1105–15.
[9] Zhou X, Xia J, Mao J, Cheng F, Qian X, Guo H. Real-world outcome and healthcare costs of relapsed or refractory multiple myeloma: a retrospective analysis from the Chinese experience. Hematology 2016;21:280–6.
[10] Blommestein HM, Verelst SG, de Groot S, Huijgens PC, Sonneveld P, Uyl-de Groot CA. A cost-effectiveness analysis of real-world treatment for elderly patients with multiple myeloma using a full disease model. Eur J Haematol 2016;96:198–208.
[11] Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. Cancer Manag Res 2013;5:37–48.
[12] Gaultney JG, Franken MG, Tan SS, Redekop WK, Huijgens PC, Sonneveld P, et al. Real-world health care costs of relapsed/refractory multiple myeloma during the era of novel cancer agents. J Clin Pharm Ther 2013;38:41–7.
[13] Gooding S, Lau IJ, Sheikh M, Roberts P, Wong J, Dickens E, et al. Double relapsed and/or refractory multiple myeloma: clinical outcomes and real world healthcare costs. PLoS One 2015;10:e0136207.
[14] Petrucci MT, Calabrese E, Levi A, Federico V, Ceccolini M, Rizzi R, et al. Cost of illness in patients with multiple myeloma in Italy: the CoMiM study. Tumori 2013;99:e193–202.
[15] NHS Health Research Authority. What approvals and decisions do I need? Available at: https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/ (accessed 11 December 2017).
[16] European Forum for Good Clinical Practice. The EFGCP Report on The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe. Available at: http://www.efgcp.eu/Downloads/EFGCPReportFiles/Italy%20definitive.pdf (accessed 11 December 2017). 2011.
[17] International Epidemiological Association. Good Epidemiological Practice (GEP).
[18] Raab MS, Cavo M, Delforge M, Driessen C, Fink L, Flinois A, et al. Multiple myeloma: practice patterns across Europe. Br J Haematol 2016;175:66–76.

[19] Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol 2016;175:252–64.
[20] National Institute for Health and Care Excellence. NICE technology appraisal guidance TA129. Bortezomib monotherapy for relapsed multiple myeloma 2007.
[21] National Institute for Health and Care Excellence. NICE technology appraisal guidance TA171. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (18 June 2009). Available at: https://www.nice.org.uk/guidance/ta171 (accessed 18 April 2016).
[22] National Institute for Health and Care Excellence. NICE technology appraisal guidance TA338. Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (25 March 2015). Available at: https://www.nice.org.uk/guidance/TA338 (accessed 18 April 2016).
[23] Department of Health. NHS reference costs 2013 to 2014 [Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014].
[24] Service C. L aboratory handbook and price list; a brief guide for clinical and laboratory staff. 2010.
[25] Press P. MedicinesComplete (online)[Available from: http://www.medicinescomplete.com/]. London.
[26] L'Assurance Maladie. Classification Commune des Actes Médicaux
[27] L'Assurance Maladie. Base des Médicaments et Infomations Tarifaires.
[28] L'Assurance Maladie. Nomenclature generale des actes professionnels (NGAP) restant en vigueur depuis la decision uncam du 11 mars 2005 presentation. 2017.
[29] L'Assurance Maladie. Biologie medicale nomencature des actes. 2017.
[30] France Ministry of Health. Echelle Nationale des Coûts [Available from: http://www.atih.sante.fr/].
[31] Kahl BS, Bartlett NL, Leonard JP, Chen L, Ganjoo K, Williams ME, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. Cancer 2010;116:106–14.
[32] Agenzia Italiana del Farmaco (AIFA). Elenco Medicinali di fascia A e H [Available from:http://www.agenziafarmaco.gov.it/it/content/elenco-medicinali-di-fascia-e-h; accessed May 15, 2015].
[33] FILE F – Regione del Veneto. Allegato A alla Dgr n. 95 del 31 gennaio 2012
[34] Ragazzo C. Regione Lombardia capo fila nel File F. Giornale Italiano di Health Technology Assessment 2009;2:119–26.
[35] Regione del Veneto: Allegato B al Decreto n. 47 del 22.5.2013 [Available from: http://www.ospedaleuniverona.it/extfiles/internet/93101/attachment/allegatob.pdf].
[36] Dani C, Ravasio R, Fioravanti L, Circelli M. Analysis of the cost-effectiveness of surfactant treatment (Curosurf®) in respiratory distress syndrome therapy in preterm infants: early treatment compared to late treatment. Italian journal of pediatrics 2014;40:40.
[37] Garattini L, Castelnuovo E, Lanzeni D, Viscarra C, (di studio DYSCO DV). Durata e costo delle visite in medicina generale: il progetto DYSCO. Farmeconomia. Health economics and therapeutic pathways 2003;4:109–14.
[38] Tarricone R, Torbica A, Franzetti F, Rosenthal VD. Hospital costs of central line-associated bloodstream infections and cost-effectiveness of closed vs. open infusion containers. The case of Intensive Care Units in Italy. Cost Effectiveness and Resource Allocation 2010;8.
[39] Vitale C, Bagnis C, Marangella M, Belloni G, Lupo M, Spina G, et al. Cost analysis of blood purification in intensive care units: continuous versus intermittent hemodiafiltration. Journal of nephrology 2003;16:572–9.
[40] Oncomip. Référentiel Traitement Myélome Multiple [updated 2011 [Available from: http://www.oncomip.org].

[41] Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.
[42] European Medicines Agency. Levact. 2011.
[43] Cheson BD, Wendtner CM, Pieper A, Dreyling M, Friedberg J, Hoelzer D, et al. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel. Clin Lymphoma Myeloma Leuk 2010;10:21–7.
[44] National Health Service Commissioning Board. National Cancer Drugs Fund List. 2013.
[45] Celgene. Revlimid (lenalidomide) summary of product characteristics. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000717/WC500056018.pdf (accessed 13 April 2016).
[46] Janssen-Cilag. Velcade® (bortezomib) summary of product characteristics. 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000539/WC500048471.pdf (accessed 13 April 2016).
[47] Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Support Care Cancer 2013;21:599–607.
[48] Kourelis TV, Kumar SK, Srivastava G, Gertz MA, Lacy MQ, Buadi FK, et al. Long-term disease control in patients with newly diagnosed multiple myeloma after suspension of lenalidomide therapy. Am J Hematol 2014;89:302–5.
[49] Gao SQ, Chen Y, Liu Q, Yang Y, Du F, Chen W. Direct medical costs associated with multiple myeloma in Chinese patients: estimations from China public health insurance claim data. Value Health 2015;18:A447–8.
[50] Potluri R, Farr AM, Hirji I, Davis C, Bhandari H, Oukessou A. Treatment sequencing patterns and costs of care in patients with relapsed/refractory multiple myeloma. Value Health 2015;18:A450.
[51] Amgen. Kyprolis (carfilzomib) summary of product characteristics. 2017.
[52] Bristol-Myers Squibb. Empliciti: summary of product charateristics. 2016.
[53] Janssen-Cilag. DARZALEX: summary of product characteristics. 2016.

Figure Captions

Figure 1. Treatment periods within each line of therapy.

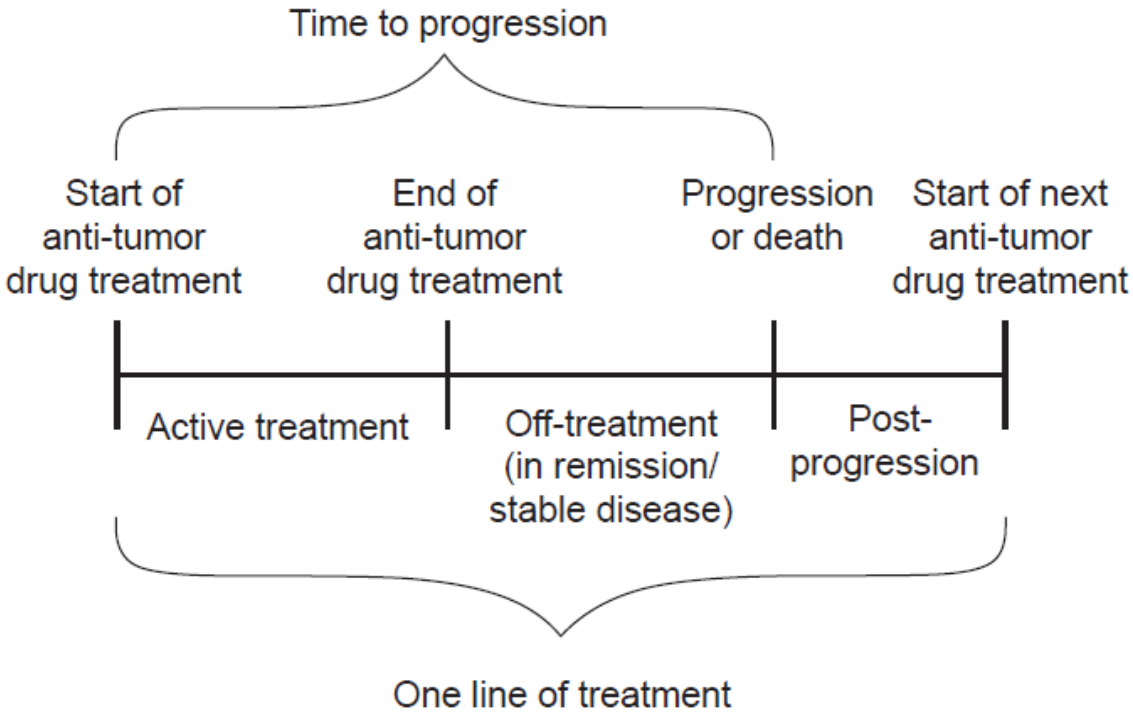
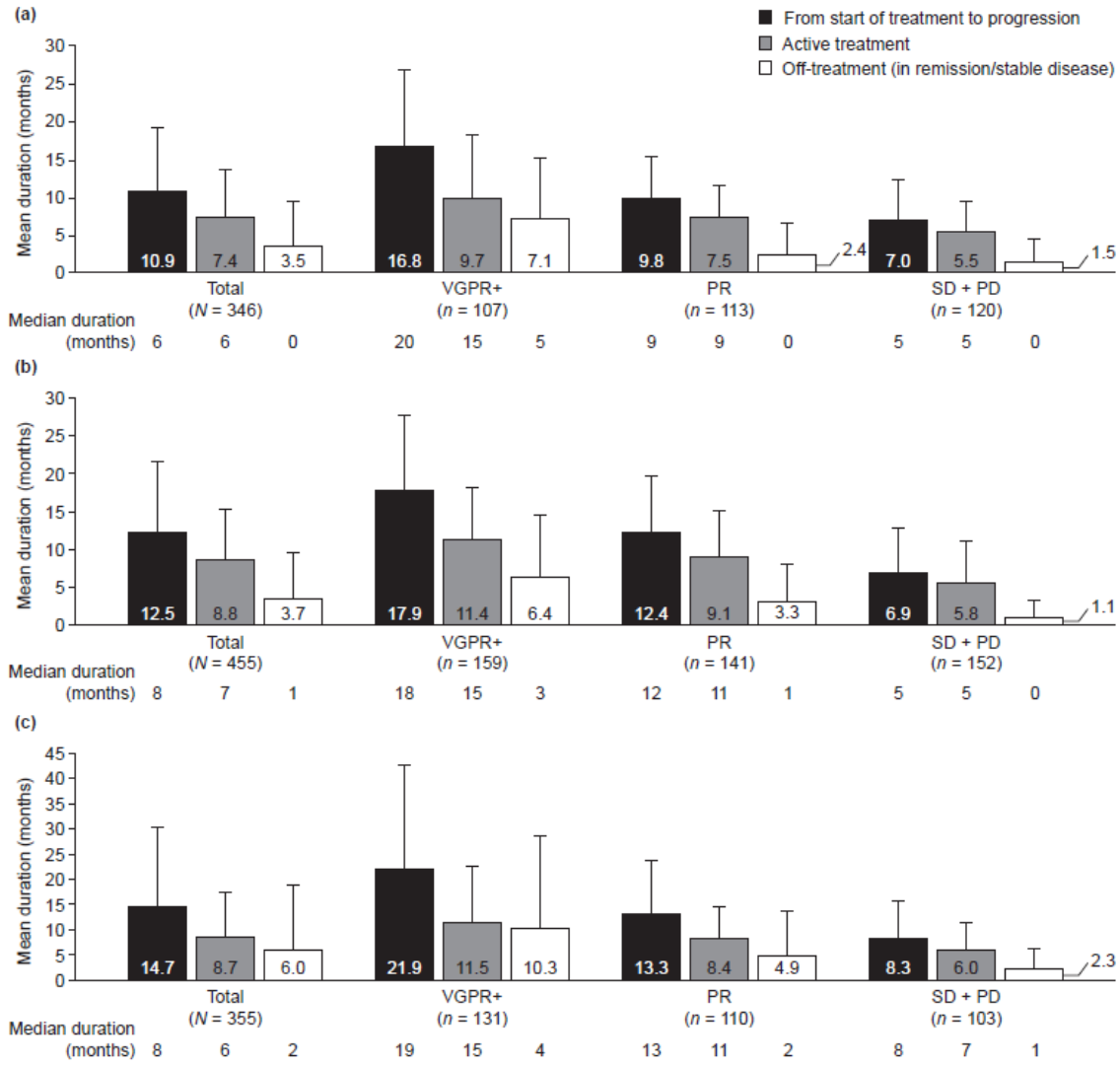


Figure 2. Mean duration of treatment periods for all patients, overall and by best response in (a) the UK, (b) France, and (c) Italy.



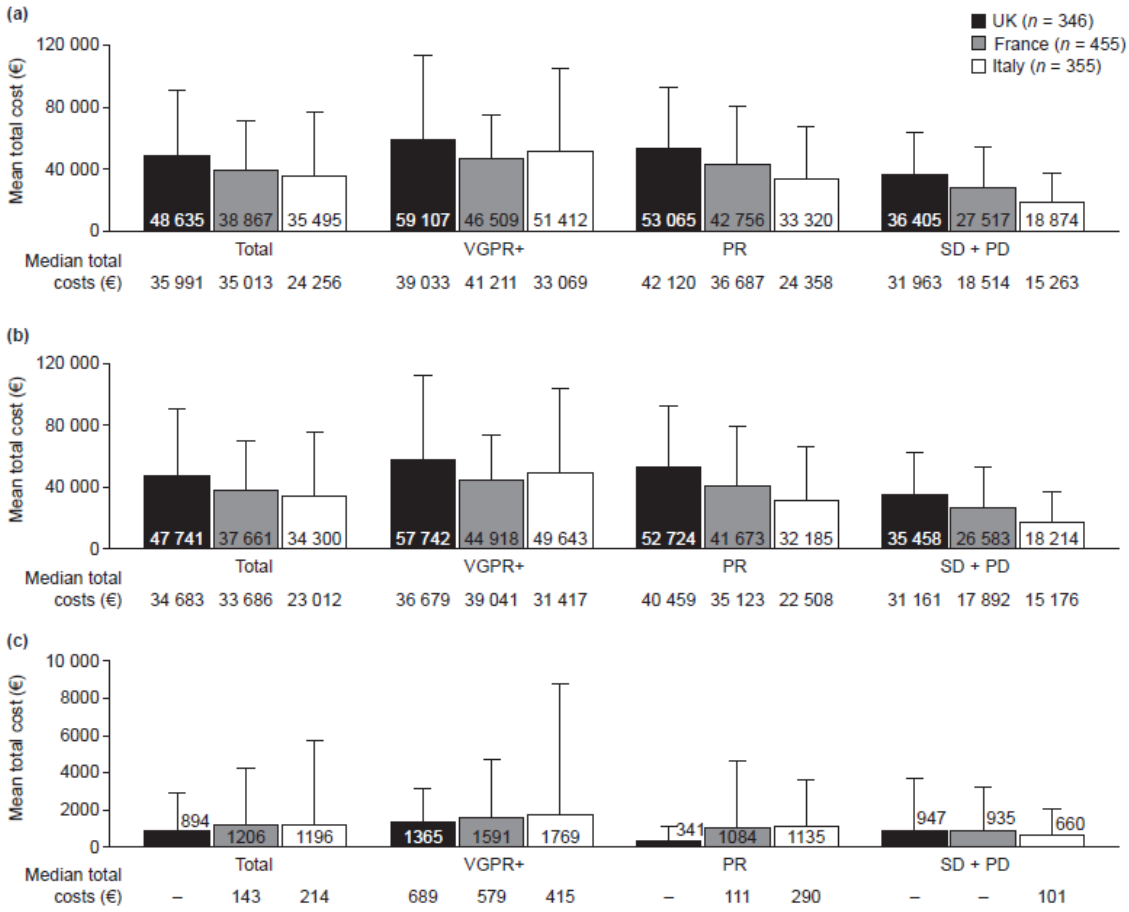
Patients who were receiving BSC and whose disease did not progress were excluded.

Error bars indicate standard error.

BSC, best supportive care; PD, progressive disease; PR, partial response; SD, stable disease; VGPR+, very good partial response or better.

Figure 3.

Total costs by treatment period and best response (a) from start of treatment until progression; (b) active treatment; (c) off-treatment (in remission/stable disease).

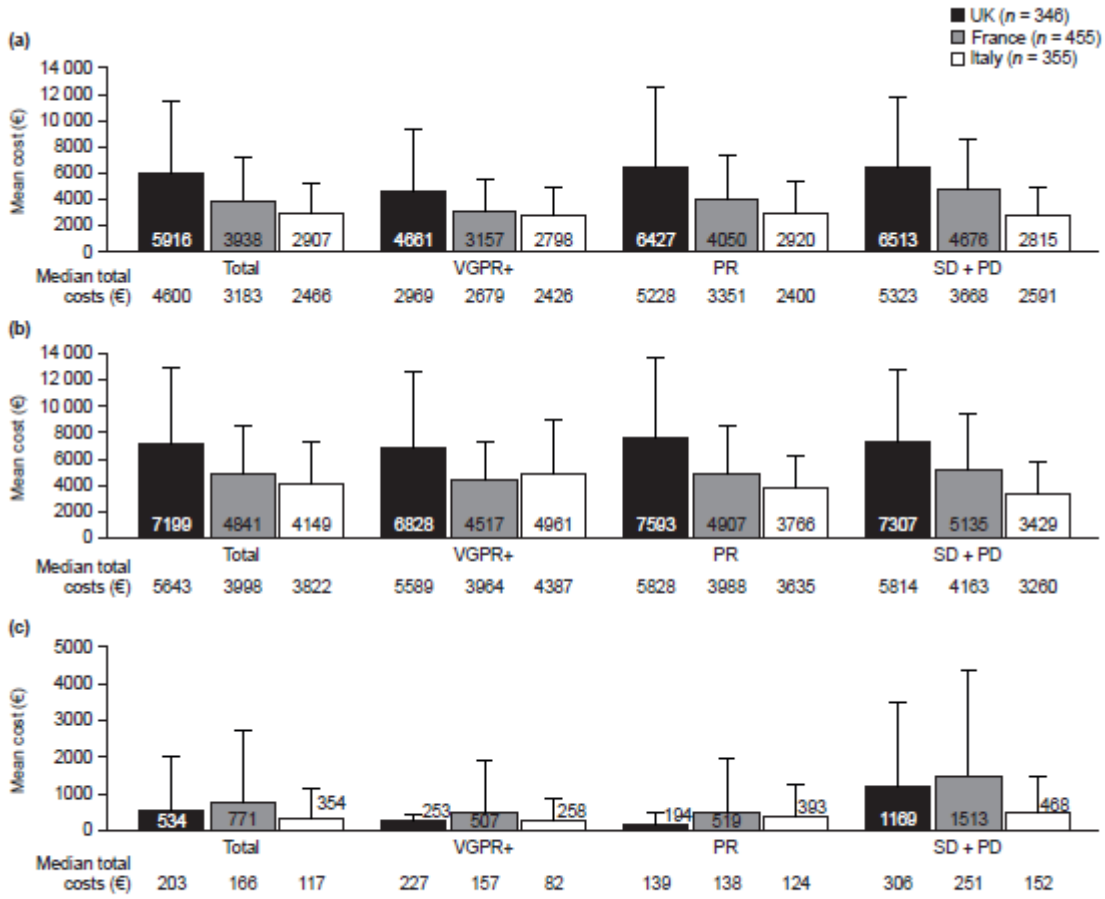


Patients who were receiving BSC and whose disease did not progress before death were excluded.

Error bars indicate standard error.

BSC, best supportive care, PD, progressive disease; PR, partial response; SD, stable disease; VGPR+, very good partial response or better.

Figure 4. Monthly costs by treatment period and best response (a) from start of treatment until progression; (b) active treatment; (c) off-treatment (in remission/stable disease).



Patients who were receiving BSC and whose disease did not progress before death were excluded.

Error bars indicate standard error.

BSC, best supportive care, PD, progressive disease; PR, partial response; SD, stable disease; VGPR+, very good partial response or better.

Figure 5. Distribution of costs (excluding cost of anti-tumor drug treatments and management of adverse events) by treatment period in (a) the UK, (b) France, and (c) Italy.

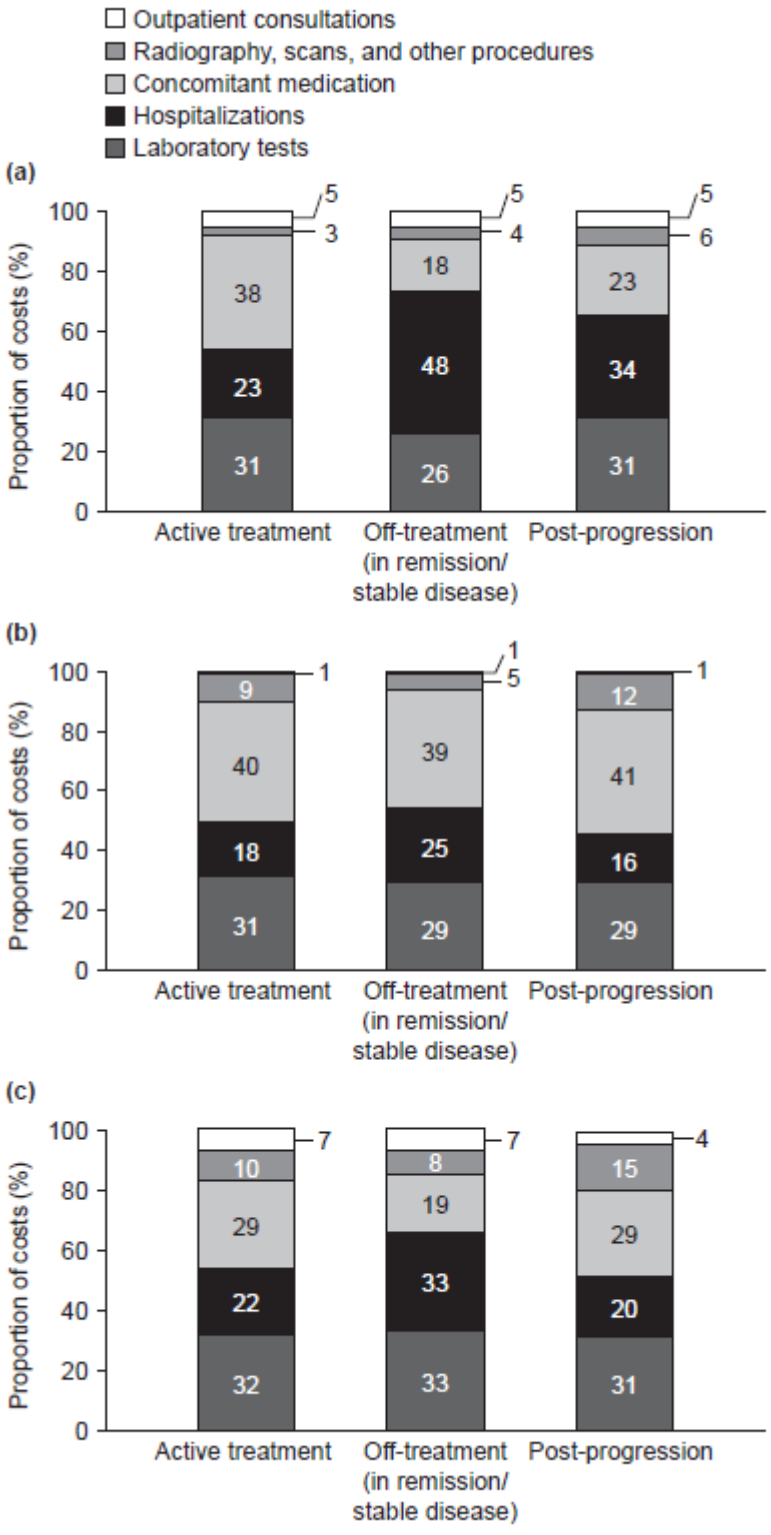
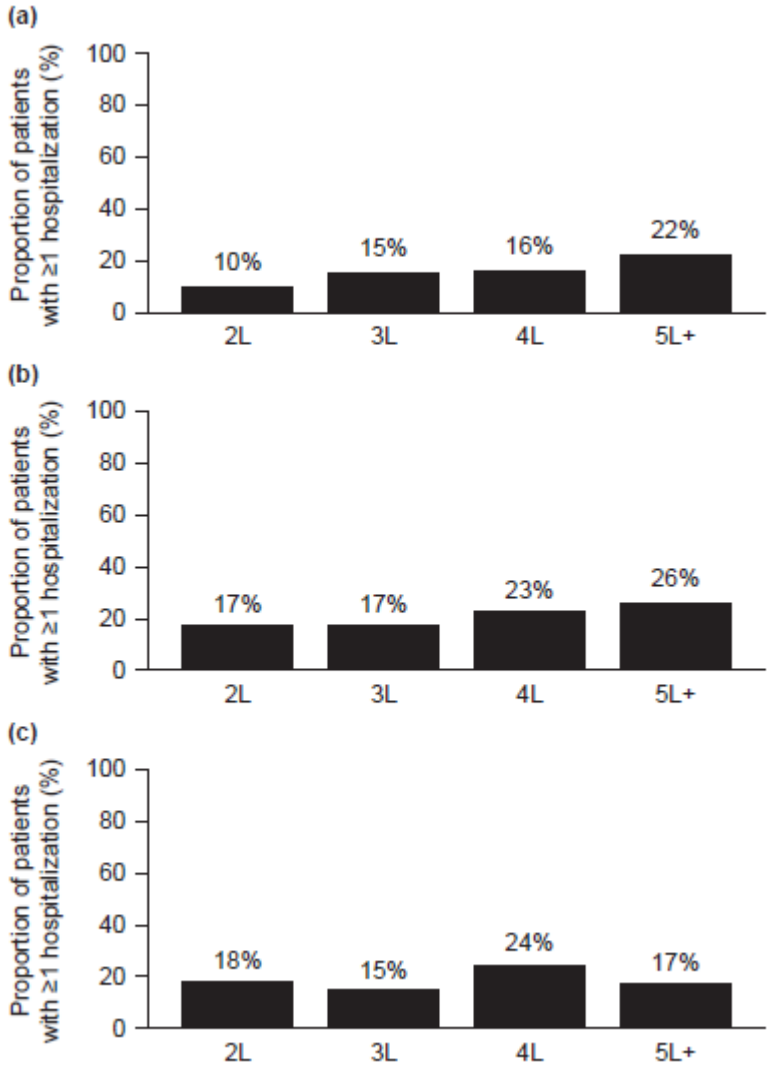
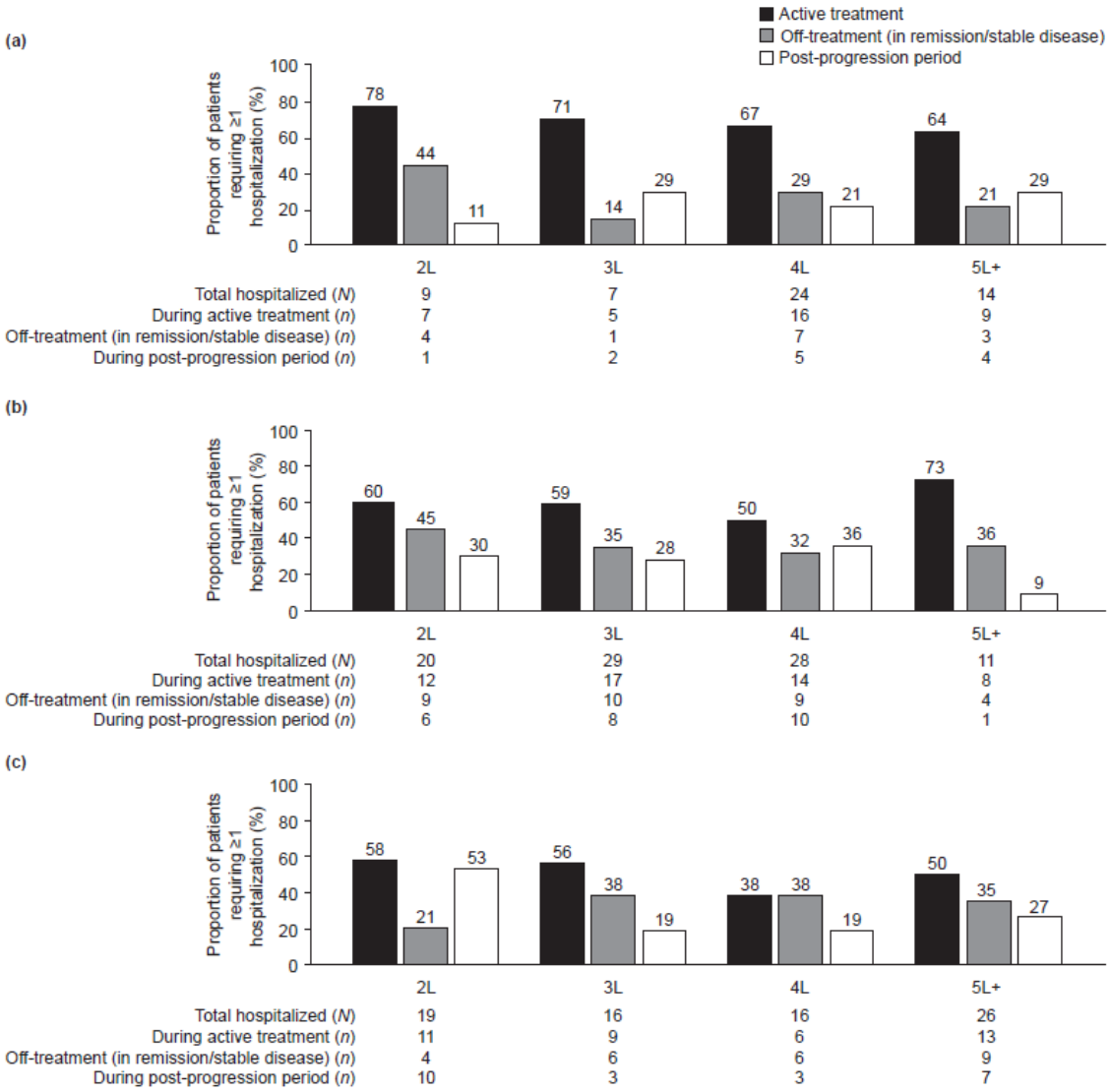


Figure 6. Proportions of patients experiencing at least one hospitalization, by therapy line in (a) the UK, (b) France, and (c) Italy.



2L, second-line treatment; 3L, third-line treatment; 4L, fourth-line treatment; 5L+, fifth-line treatment and beyond.

Figure 7. Treatment periods during which hospitalizations[a] occurred, by therapy line in (a) the UK, (b) France, and (c) Italy.



[a]Individual patients may have experienced hospitalization in more than one period.

2L, second-line treatment; 3L, third-line treatment; 4L, fourth-line treatment; 5L+, fifth-line treatment and beyond.

Table 1. Baseline demographics and disease characteristics of all patients, according to treatment and line of therapy

UK											
Treatment line	**2**		**3**				**4**				**5+**
Pre-specified treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country availability	Y	Y	Y	N	N	N	Y	N	Y	Y	Y
Patient number (n)	41	46	46	–	–	–	67	–	59	24	63
Male	68%	59%	63%	–	–	–	48%	–	66%	42%	59%
Mean BSA (m^2)	1.8	1.8	1.8	–	–	–	1.8	–	1.8	1.6	1.8
Mean weight (kg)	76	74	74	–	–	–	72	–	74	67	73
ISS stage at diagnosis											
I	10%	7%	9%	–	–	–	13%	–	5%	8%	11%
II	42%	61%	50%	–	–	–	49%	–	54%	50%	57%
III	49%	33%	41%	–	–	–	37%	–	41%	42%	32%
Mean age (years)											
At diagnosis	62	64	65	–	–	–	63	–	62	62	62
At treatment initiation	63	66	68	–	–	–	67	–	65	68	69
At last completed line of therapy	63	66	68	–	–	–	67	–	65	63	65
Mean time from diagnosis (months)											
To initiation of line	21	27	36	–	–	–	41	–	44	65	85
To end of last completed line of therapy	29	33	47	–	–	–	50	–	51	46	62
Median time from diagnosis (months)											
To end of last completed line of therapy	22	27	36	–	–	–	46	–	43	43	54
ECOG PS at initiation of line											
0–1	90%	96%	85%	_	_	_	84%	_	85%	83%	67%
≥ 2	10%	4%	15%	–	–	–	16%	–	15%	17%	33%
Normal renal function at initiation of line	32%	44%	39%	–	–	–	33%	–	37%	21%	22%
Previous stem cell transplant	10%	17%	15%	–	–	–	19%	–	15%	33%	30%
France											
Treatment line	**2**		**3**				**4**				**5+**

Pre-specified treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country availability	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Patient number (n)	65	51	48	44	37	45	29	–	49	44	43
Male	63%	63%	52%	50%	49%	64%	52%	–	57%	46%	56%
Mean BSA (m^2)	1.7	1.8	1.8	1.7	1.7	1.7	1.8	–	1.8	1.7	1.7
Mean weight (kg)	71	73	73	70	67	71	70	–	74	69	70
ISS stage at diagnosis											
I	11%	10%	17%	21%	11%	13%	7%	–	12%	18%	16%
II	32%	43%	27%	30%	19%	31%	41%	–	25%	25%	21%
III	57%	47%	56%	50%	70%	56%	52%	–	63%	57%	63%
Mean age (years)											
At diagnosis	68	66	68	65	64	65	62	–	61	64	59
At treatment initiation	72	70	73	70	68	69	68	–	67	69	66
At last completed line of therapy	71	69	72	70	68	69	67	–	67	69	66
Mean time from diagnosis (months)											
To initiation of line	28	36	42	48	37	40	58	–	58	54	79
To end of last completed line of therapy	41	44	54	57	44	47	69	–	66	61	84
Median time from diagnosis (months)											
To end of last completed line of therapy	23	29	27	29	19	21	36	–	28	32	55
ECOG PS at initiation of line											
0–1	74%	82%	65%	71%	68%	71%	69%	_	59%	46%	40%
≥ 2	26%	18%	35%	30%	32%	29%	31%	–	41%	55%	61%
Normal renal function at initiation of line	48%	45%	35%	39%	43%	38%	48%	–	25%	18%	16%
Previous stem cell transplantation	20%	22%	23%	25%	19%	24%	31%	–	41%	27%	47%
Italy											
Treatment line	2		3				4				5+
Pre-specified treatment	Len	Bort	Len	Bort	Pom	Bend	Len	Bort	Pom	Bend	
Country availability	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Patient number (n)	46	44	40	39	–	31	39	33	–	36	47
Male	63%	61%	38%	49%	–	58%	64%	61%	–	44%	75%

Mean BSA (m^2)	1.7	1.7	1.7	1.7	–	1.7	1.7	1.8	–	1.7	1.8
Mean weight (kg)	69	70	68	71	–	69	70	72	–	70	73
ISS stage at diagnosis											
I	26%	18%	15%	21%	–	10%	15%	21%	–	19%	19%
II	44%	48%	43%	39%	–	45%	39%	30%	–	56%	36%
III	30%	34%	43%	41%	–	45%	46%	49%	–	25%	45%
Mean age (years)											
At diagnosis	65	66	65	64	–	63	60	60	–	60	61
At treatment initiation	67	68	69	68	–	67	65	65	–	63	65
At last completed line of therapy	67	68	69	68	–	67	65	65	–	68	69
Mean time from diagnosis (months)											
To initiation of line	28	31	45	47	–	46	63	56	–	41	57
To end of last completed line of therapy	38	38	58	53	–	54	75	63	–	73	92
Median time from diagnosis (months)											
To end of last completed line of therapy	33	33	50	46	–	49	68	55	–	65	86
ECOG PS at initiation of line											
0–1	61%	68%	65%	62%	_	61%	49%	61%	_	44%	26%
≥ 2	39%	32%	35%	39%	–	39%	51%	39%	–	56%	75%
Normal renal function at initiation of line	57%	59%	40%	39%	–	42%	39%	36%	–	44%	23%
Previous stem cell transplantation	28%	36%	38%	33%	–	19%	46%	39%	–	36%	43%

bend, bendamustine; bort, bortezomib; BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; len, lenalidomide; pom, pomalidomide

Table 2. Best response to anti-tumor treatment, by therapy line

UK											
Treatment line	**2**		**3**				**4**				**5+**
Pre-specified treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country availability	Y	Y	Y	N	N	N	Y	N	Y	Y	Y
Patient number (n)	41	46	46	–	–	–	67	–	59	24	63
Response (%)											
VGPR+	39	54	39	–	–	–	37	–	15	37	8
CR	7	4	11	–	–	–	3	–	0	8	0
VGPR	32	50	28	–	–	–	34	–	15	29	8
PR	37	30	22	–	–	–	33	–	41	25	35
SD + PD	24	13	39	–	–	–	25	–	44	38	54
Not evaluable/not reported	0	2	0	–	–	–	5	–	0	0	3
France											
Treatment line	2		3				4				5+
Pre-specified treatment	Len	Bort	Len	Bort	Pom	Bend	Len	Bort	Pom	Bend	
Country availability	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Patient number (n)	65	51	48	44	37	45	29	–	49	44	43
Response (%)											
VGPR+	48	53	56	52	19	28	48	–	14	11	12
CR	14	16	8	9	3	4	7	–	0	2	0
VGPR	34	37	48	43	16	24	41	–	14	9	12
PR	32	24	25	23	32	49	31	–	31	48	16
SD + PD	20	24	18	23	46	22	21	–	55	41	70
Not evaluable/not reported	0	0	0	2	3	0	0	–	0	0	2
Italy											
Treatment line	2		3				4				5+
Pre-specified treatment	Len	Bort	Len	Bort	Pom	Bend	Len	Bort	Pom	Bend	
Country availability	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Patient number (n)	46	44	40	39	–	31	39	33	–	36	47

Response (%)											
VGPR+	46	50	43	33	–	42	39	36	–	25	19
CR	11	14	8	8	–	10	3	6	–	3	2
VGPR	35	36	35	26	–	32	36	30	–	22	17
PR	28	27	33	36	–	29	36	33	–	39	21
SD + PD	22	19	25	30	–	29	20	24	–	31	58
Not evaluable/not reported	4	5	0	0	–	0	5	6	–	6	2

Values shown are percentages of patients.

bend, bendamustine; bort, bortezomib; CR, complete response; len, lenalidomide; PD, progressive disease; pom, pomalidomide; PR, partial response; SD, stable disease; VGPR, very good partial response; VGPR+, very good partial response or better (VGPR + CR + stringent CR).

Table 3. Duration of treatment periods by line and treatment.

UK											
Treatment line	**2**		**3**				**4**				**5+**
Pre-Specified Treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country Availability	Y	Y	Y	N	N	N	Y	N	Y	Y	Y
Patient number (n)	41	46	46	–	–	–	67	–	59	24	63
Period duration by treatment (months)											
Active treatment											
Mean	8.4	5.9	10.2	–	–	–	9.3	–	6.7	5.5	5.4
Median	7.0	5.5	7.5	–	–	–	7.0	–	6.0	5.0	5.0
Off treatment											
Mean	4.1	7.2	4.9	–	–	–	2.5	–	2.7	2.6	1.5
Median	1.0	5.0	0.0	–	–	–	0.0	–	0.0	1.0	0.0
Time to progression/Pre-progression											
Mean	12.5	13.1	15.1	–	–	–	11.8	–	9.4	8.0	6.9
Median	10.0	11.5	13.0	–	–	–	9.0	–	9.0	8.0	6.0
Post-progression											
Patient number (n)	4	24	54	17	8	12	9		17	13	
Mean	3.0	6.2	4.2	2.6	3.1	5.5	1.9	–	3.2	2.8	–
Median	2.5	2.0	2.0	2.0	2.0	2.0	1.0	–	2.0	2.0	–
Period duration by line (months)											
Active treatment											
Mean	–	7.1	–	–	–	10.2	–	–	–	7.6	–
Median	–	6.0	–	–	–	7.5	–	–	–	6.0	–
Off treatment											
Mean	–	5.7	–	–	–	4.9	–	–	–	2.6	–
Median	–	2.0	–	–	–	0	–	–	–	0	–
Time to progression/Pre-progression											

Mean	–	12.8	–	–	–	15.1	–	–	–	10.3	–
Median	–	11.0	–	–	–	13.0	–	–	–	9.0	–
Post-progression											
Mean	–	2.9	–	–	–	3.9	–	–	–	2.4	–
Median	–	1.0	–	–	–	1.0	–	–	–	1.0	–
France											
Treatment line	**2**		**3**				**4**				**5+**
Pre-Specified Treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country Availability	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Patient number (n)	65	51	48	44	37	45	29	–	49	44	43
Period duration by treatment (months)											
Active treatment											
Mean	12.7	8.1	12.4	8.5	7.3	7.0	11.6	–	7.6	6.6	5.0
Median	11.0	8.0	11.0	8.0	6.0	5.0	10.0	–	6.0	6.0	4.0
Off treatment											
Mean	4.2	7.0	4.1	5.5	1.4	4.8	2.2	–	1.2	2.9	1.6
Median	1.0	5.0	1.0	3.0	0.0	5.0	0.0	–	0.0	1.0	0.0
Time to progression/Pre-progression											
Mean	17.0	15.1	16.5	14.0	8.6	11.9	13.8	–	8.8	9.5	6.6
Median	14.0	13.0	14.0	13.0	7.0	11.0	12.0	–	7.0	9.0	5.0
Post-progression											
Patient number (n)	85	51	18	23	18	22	4	6	10	8	–
Mean	6.0	4.9	2.0	4.5	3.6	4.0	4.0	2.7	3.7	3.0	–
Median	2.0	2.0	1.0	2.0	2.0	2.0	2.0	1.0	1.5	2.0	–
Period duration by line (months)											
Active treatment											

Mean	–	10.7	–	–	–	8.9	–	–	–	8.2	–
Median	–	9.0	–	–	–	7.5	–	–	–	6.0	–
Off treatment											
Mean	–	5.5	–	–	–	4.1	–	–	–	2.1	–
Median	–	1.5	–	–	–	1.0	–	–	–	1.0	–
Time to progression/Pre-progression											
Mean	–	16.2	–	–	–	13.0	–	–	–	10.2	–
Median	–	14.0	–	–	–	11.0	–	–	–	9.0	–
Post-progression											
Mean	–	2.4	–	–	–	4.0	–	–	–	2.6	–
Median	–	1.0	–	–	–	1.0	–	–	–	1.0	–
Italy											
Treatment line	**2**		**3**				**4**				**5+**
Pre-Specified Treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country Availability	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Patient number (n)	46	44	40	39	–	31	39	33	–	36	47
Period duration by treatment (months)											
Active treatment											
Mean	10.7	6.5	13.2	6.5	–	7.8	12.3	6.3	–	7.4	7.2
Median	9.0	6.0	9.0	6.0	–	5.0	8.0	6.0	–	6.0	5.0
Off treatment											
Mean	4.5	9.0	4.3	10.6	–	6.6	4.9	4.6	–	8.4	2.0
Median	1.0	3.0	1.5	4.0	–	2.0	2.0	2.0	–	3.0	1.0
Time to progression/Pre-progression											
Mean	15.2	15.5	17.5	17.2	–	14.4	17.2	10.9	–	15.8	9.2
Median	12.0	9.0	14.5	11.0	–	9.0	13.0	9.0	–	10.5	7.0
Post-progression											
Patient number (n)	32	43	32	32	3	18	4	9	5	10	–

Mean	5.3	4.4	8.3	6.3	1.3	4.6	8.3	4.4	4.2	3.5	–
Median	3.0	2.0	2.0	2.5	1.0	3.0	9.5	3.0	3.0	1.5	–
Period duration by line (months)											
Active treatment											
Mean	–	8.7	–	–	–	9.3	–	–	–	8.8	–
Median	–	7.0	–	–	–	6.0	–	–	–	6.0	–
Off treatment											
Mean	–	6.7	–	–	–	7.2	–	–	–	6.0	–
Median	–	2.0	–	–	–	3.0	–	–	–	3.0	–
Time to progression/Pre-progression											
Mean	–	15.3	–	–	–	16.5	–	–	–	14.8	–
Median	–	12.0	–	–	–	12.0	–	–	–	11.5	–
Post-progression											
Mean	–	2.7	–	–	–	5.1	–	–	–	5.3	–
Median	–	1.0	–	–	–	2.0	–	–	–	2.0	–

5L+, fifth-line treatment and beyond; bend, bendamustine; bort, bortezomib; CR, complete response; len, lenalidomide; PD, progressive disease; pom, pomalidomide; PR, partial response; SD, stable disease; VGPR, very good partial response; VGPR+, very good partial response or better (VGPR + CR + stringent CR).
The active treatment period was the time between initiation and discontinuation of the treatment.
The off-treatment period was the time after the patient had discontinued the treatment until identification of progression.
The pre-progression period was the time between initiation of treatment and diagnosis of progression.
The post-progression period was the time from disease progression until the next line of treatment was initiated (not reported for 5L+).

Table 4. Total and monthly costs per resource used during the active treatment period, by therapy line.

UK											
Treatment line	**2**		**3**				**4**				**5+**
Pre-Specified Treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country Availability	Y	Y	Y	N	N	N	Y	N	Y	Y	Y
Patient number (n)	41	46	46	–	–	–	67	–	59	24	63
Mean resource costs (€)											
Anti-myeloma drug treatment	44 149	22 345	55 216	–	–	–	52 712	–	76 279	17 119	28 643
Concomitant medications	1279	680	1478	–	–	–	1102	–	881	761	887
Hospitalizations	548	140	642	–	–	–	517	–	566	321	876
Outpatient consultations	33	27	38	–	–	–	39	–	26	23	22
Laboratory tests	758	646	1171	–	–	–	1025	–	641	456	598
Radiography, scans, other	312	156	297	–	–	–	289	–	202	169	157
Total costs by treatment (€)											
Mean (€)	47 357	23 978	58 870	–	–	–	55 528	–	78 595	18 846	31 530
Median (€)	35 185	21 776	41 821				39 957		74 304	8940	12 003
Total costs by line (€)											
Mean (€)		34 995				58 868				58 730	31 048
Median (€)		31 810				41 914				46 591	11 989
Monthly resource costs (€)											
Anti-myeloma drug treatment	6170	3832	5661	–	–	–	6824	–	13 172	4014	5250
Concomitant medications	321	212	187	–	–	–	246	–	331	226	400
Hospitalizations	610	-	784	–	–	–	544	–	1942	618	1939
Outpatient consultations	5	6	4	–	–	–	6	–	6	5	6
Laboratory tests	83	112	94	–	–	–	112	–	108	94	119
Radiography, scans, other	94	58	85	–	–	–	94	–	85	75	110
Monthly costs by treatment (€)											
Mean (€)	6544	4094	5988	–	–	–	7159	–	13 651	4378	5789
Median (€)	5812	3870	5825	–	–	–	5739	–	12 740	1833	2491
Monthly costs by line (€)											
Mean (€)		5247				5988				9282	5789

Median (€)		5028				5825				7021	2491
France											
Treatment line	2		3				4				5+
Pre-Specified Treatment	Len	Bort	Len	Bort	Pom	Bend	Len	Bort	Pom	Bend	
Country Availability	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Patient number (n)	65	51	48	44	37	45	29	–	49	44	43
Mean resource costs (€)											
Anti-myeloma drug treatment	38 739	30 841	41 827	32 847	62 772	9427	42 152	–	60 686	87081	20 869
Concomitant medications	1182	1250	1495	766	910	2447	1347	–	1554	2564	1241
Hospitalizations	1038	2018	750	260	332	451	197	–	659	2118	1172
Outpatient consultations	238	219	244	250	170	203	246	–	189	137	144
Laboratory tests	1458	1005	1450	916	1001	925	1404	–	1362	1417	958
Radiography, scans, other	102	139	125	158	66	103	166	–	145	126	150
Total costs by treatment (€)											
Mean (€)	42 584	35 447	45 798	35 101	65 289	13 437	45 466	–	64 468	15 112	24 051
Median (€)	37 721	35 617	42 912	34 914	55 390	9510	38 654		55 232	9786	5691
Total costs by line (€)											
Mean (€)		39127				38075				41900	20004
Median (€)		35848				35331				29932	5691
Monthly resource costs (€)											
Anti-myeloma drug treatment	3371	4171	3409	4546	9179	1831	3754	–	8712	1354	4098
Concomitant medications	231	299	192	198	305	648	279	–	391	616	435
Hospitalizations	2448	2762	485	1788	666	1317	477	–	1596	3031	1420
Outpatient consultations	24	33	22	36	29	38	24	–	33	27	39
Laboratory tests	130	138	119	130	140	157	121	–	193	193	205
Radiography, scans, other	39	62	38	64	30	88	47	–	71	94	184
Monthly costs by treatment (€)											
Mean (€)	3742	4914	3757	4809	9299	2421	4065	–	9361	2526	4067
Median (€)	3747	4653	3852	4399	9377	1488	3978	–	9921	1697	2116
Monthly costs by line (€)											
Mean (€)		4261				4856				5637	4067

Median (€)		3995				4010				4264	2116
Italy											
Treatment line	2		3				4				5+
Pre-Specified Treatment	Len	Bort	Len	Bort	Pom	Bend	Len	Bort	Pom	Bend	
Country Availability	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Patient number (n)	46	44	40	39	–	31	39	33	–	36	47
Mean resource costs (€)											
Anti-myeloma drug treatment	55 044	25 216	67 994	23 898	–	9423	63 215	25 748	–	6224	7296
Concomitant medications	964	586	709	477	–	610	774	410	–	688	472
Hospitalizations	435	683	125	0	–	925	642	455	–	695	582
Outpatient consultations	169	207	216	128	–	120	212	106	–	94	69
Laboratory tests	818	524	829	503	–	683	559	478	–	518	440
Radiography, scans, other	259	137	308	205	–	208	306	140	–	186	218
Total costs by treatment (€)											
Mean (€)	57 711	27 360	70 260	25 274	–	11 956	65 813	27 321	–	8454	8983
Median (€)	47 233	22 892	42 956	19 767		8075	47 284	22 155		6848	5438
Total costs by line (€)											
Mean (€)		42 873				37879				34 874	8185
Median (€)		30 324				23346				22 048	4508
Monthly resource costs (€)											
Anti-myeloma drug treatment	5490	4347	5595	3865	–	1735	5573	4413	–	1275	1768
Concomitant medications	191	179	129	180	–	179	118	123	–	181	186
Hospitalizations	781	901	2503	0	–	2027	566	1020	–	848	2453
Outpatient consultations	27	41	25	34	–	34	22	26	–	27	35
Laboratory tests	91	109	86	98	–	91	64	86	–	91	96
Radiography, scans, other	43	46	28	46	–	66	34	39	–	46	80
Monthly costs by treatment (€)											
Mean (€)	5765	4690	5822	4064	–	2307	5804	4684	–	1577	2111
Median (€)	5698	3654	5595	3625	–	1333	5950	4175	–	1015	858
Monthly costs by line (€)											
Mean (€)		5239				4208				4047	2111

Median (€)	4756	3904	3471	858

An exchange rate of £1 = €1.3931 was used (exchange rate on 1 June 2015).
bend, bendamustine; bort, bortezomib; len, lenalidomide; pom, pomalidomide.

Table 5. Adverse events and hospitalizations of patients (%) receiving anti-tumor treatment.

Country	UK				France				Italy			
Pre-specified treatment	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**
Country availability	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**
Patient number (n)	154	46	59	–	142	95	86	89	125	116	–	67
Adverse event (n)												
None	88	91	86	–	87	84	79	74	72	68	–	64
Anemia	1	0	3	–	5	2	5	9	6	9	–	8
Bone fracture	0	4	3	–	6	3	8	6	8	7	–	10
Cardiac dysfunction	0	0	3	–	1	0	1	2	2	4	–	0
Deep vein thrombosis	1	0	0	–	1	0	6	2	0	4	–	0
Fatigue	2	0	2	–	2	2	0	6	4	8	–	6
Hypercalcemia	1	0	2	–	1	2	4	6	5	1	–	2
Neuropathy	2	2	0	–	2	3	5	2	3	7	–	8
Neutropenia	3	0	2	–	3	0	1	5	6	3	–	9
Pain	1	2	3	–	1	2	2	5	10	8	–	8
Renal impairment	4	2	3	–	0	1	6	3	2	3	–	3
Thrombocytopenia	3	0	3	–	2	0	5	6	4	2	–	0
Upper respiratory tract infection	4	2	3	–	1	2	8	3	6	5	–	8
Hospitalizations (n)	22	3	11		23	15	17	22	23	20		15
0	87.7%	91.3%	86.4%		86.6%	84.2%	79.1%	74.2%	72.0%	68.1%		64.2%
1	7.8%	4.3%	10.2%		9.2%	12.6%	11.6%	11.2%	15.2%	14.7%		19.4%
≥ 2	4.5%	4.3%	3.4%		4.2%	3.2%	9.3%	14.6%	12.8%	17.2%		16.4%

bend, bendamustine; bort, bortezomib; len, lenalidomide; pom, pomalidomide.

Supplementary Table 1. Treatment combinations received by treatment line and country.

UK											
Treatment line	**2**		**3**				**4**				**5+**
Pre-specified treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country availability	Y	Y	Y	N	N	N	Y	N	Y	Y	Y
Patient number (n)	41	46	46	–	–	–	67	–	59	24	63
Concomitant treatment											
Total combinations	10 (24)	15 (33)	10 (22)	–	–	–	13 (19)	–	4 (7)	6 (25)	19 (30)
Adriamycin/doxorubicin	1 (2)	3 (7)	0 (0)	–	–	–	0 (0)	–	0 (0)	0 (0)	1 (2)
Bend	2 (5)	0 (0)	3 (7)	–	–	–	3 (5)	–	2 (3)	24 (100)	17 (27)
Bort	0 (0)	46 (100)	0 (0)	–	–	–	1 (2)	–	0 (0)	1 (4)	8 (13)
Cyclophosphamide	7 (17)	10 (22)	7 (15)	–	–	–	7 (10)	–	2 (3)	0 (0)	7 (11)
Dexamethasone	19 (46)	26 (57)	22 (48)	–	–	–	28 (42)	–	26 (44)	8 (33)	29 (46)
Len	41 (100)	0 (0)	46 (100)	–	–	–	67 (100)	–	0 (0)	2 (8)	0 (0)
Melphalan	0 (0)	1 (2)	0 (0)	–	–	–	1 (2)	–	0 (0)	0 (0)	6 (10)
Pom	0 (0)	0 (0)	0 (0)	–	–	–	1 (2)	–	59 (100)	1 (4)	20 (32)
Prednisone	2 (5)	4 (9)	2 (4)	–	–	–	1 (2)	–	3 (5)	4 (17)	10 (16)
Thalidomide	0 (0)	2 (4)	0 (0)	–	–	–	0 (0)	–	0 (0)	2 (8)	7 (11)
Vincristine	0 (0)	0 (0)	0 (0)	–	–	–	1 (2)	–	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	–	–	–	0 (0)	–	0 (0)	0 (0)	1 (2)
France											
Treatment line	**2**		**3**				**4**				**5+**
Pre-specified treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country availability	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Patient number (n)	65	51	48	44	37	45	29	–	49	44	43
Concomitant treatment											
Total combinations	5 (8)	17 (33)	2 (4)	15 (34)	5 (14)	7 (16)	1 (3)	–	3 (6)	4 (9)	10 (23)

Adriamycin/doxorubicin	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	3 (7)
Bend	1 (2)	2 (4)	1 (2)	0 (0)	1 (3)	45 (100)	0 (0)	–	1 (2)	44 (100)	12 (28)
Bort	5 (8)	51 (100)	1 (2)	44 (100)	0 (0)	7 (16)	0 (0)	–	1 (2)	4 (9)	6 (14)
Cyclophosphamide	0 (0)	7 (14)	1 (2)	7 (16)	3 (8)	0 (0)	0 (0)	–	2 (4)	0 (0)	8 (19)
Dexamethasone	47 (72)	37 (73)	31 (65)	31 (71)	24 (65)	14 (31)	21 (72)	–	33 (67)	13 (30)	22 (51)
Len	65 (100)	1 (2)	48 (100)	1 (2)	0 (0)	0 (0)	29 (100)	–	0 (0)	0 (0)	4 (9)
Melphalan	0 (0)	6 (12)	0 (0)	6 (14)	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	1 (2)
Pom	0 (0)	0 (0)	0 (0)	0 (0)	37 (100)	0 (0)	1 (3)	–	49 (100)	0 (0)	12 (28)
Prednisone	3 (5)	8 (16)	2 (4)	3 (7)	2 (5)	13 (29)	1 (3)	–	5 (10)	7 (16)	4 (9)
Thalidomide	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	2 (5)
Vincristine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	2 (5)
Other	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	–	0 (0)	0 (0)	2 (5)
Italy											
Treatment line	**2**		**3**				**4**				**5+**
Pre-specified treatment	**Len**	**Bort**	**Len**	**Bort**	**Pom**	**Bend**	**Len**	**Bort**	**Pom**	**Bend**	
Country availability	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Patient number (n)	46	44	40	39	–	31	39	33	–	36	47
Concomitant treatment											
Total combinations	1 (2)	9 (21)	0 (0)	12 (31)	–	8 (26)	0 (0)	7 (21)	–	6 (17)	13 (28)
Adriamycin/doxorubicin	0 (0)	1 (2)	0 (0)	3 (8)	–	0 (0)	0 (0)	0 (0)	–	0 (0)	3 (6)
Bend	0 (0)	1 (2)	0 (0)	1 (3)	–	31 (100)	0 (0)	2 (6)	–	36 (100)	11 (23)
Bort	1 (2)	44 (100)	0 (0)	39 (100)	–	7 (23)	0 (0)	33 (100)	–	5 (14)	8 (17)
Cyclophosphamide	0 (0)	1 (2)	0 (0)	4 (10)	–	0 (0)	0 (0)	3 (9)	–	0 (0)	8 (17)
Dexamethasone	22 (48)	17 (39)	20 (50)	22 (56)	–	12 (39)	11 (28)	18 (55)	–	6 (17)	17 (36)
Len	46 (100)	2 (5)	40 (100)	0 (0)	–	1 (3)	39 (100)	0 (0)	–	2 (6)	4 (9)
Melphalan	0 (0)	3 (7)	0 (0)	4 (10)	–	0 (0)	0 (0)	2 (6)	–	0 (0)	2 (4)

Pom	0 (0)	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	0 (0)	–	0 (0)	7 (15)
Prednisone	4 (9)	4 (9)	3 (8)	4 (10)	–	2 (7)	4 (10)	2 (6)	–	2 (6)	7 (15)
Thalidomide	0 (0)	1 (2)	0 (0)	2 (5)	–	0 (0)	0 (0)	0 (0)	–	0 (0)	2 (4)
Vincristine	0 (0)	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	0 (0)	–	0 (0)	1 (2)
Other	0 (0)	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	0 (0)	–	0 (0)	2 (4)

Values are n (%).
bend, bendamustine; bort, bortezomib; len, lenalidomide; NA, not applicable; pom, pomalidomide.

Supplementary Table 2. Drug unit costs by country.

Country	UK (£)	France (€)	Italy (€)
Pre-specified treatments			
Bendamustine	25 mg vial = 69.45	100 mg = 279.56	100 mg × 5 = 1296.75
Lenalidomide	21 pills of 10 mg = 3780.00	1 pill of 10 mg = 166.87	21 pills of 10 mg = 5041.37
Bortezomib	3.5 mg vial = 762.38	3.5 mg = 1065.77	3.5 mg = 1173.25
Pomalidomide	21 capsules of 1/2/3/4 mg = 8884.00	1 pill of 3 mg = 433.93	n/a
Anti-myeloma drugs			
Thalidomide	28 pills of 50 mg = 298.48	1 pill of 50 mg = 12.15	28 pills of 50 mg = 346
Adriamycin/Doxorubicine		10 mg = 6.13	10 mg = 9.03
Cyclophosphamide		500 mg = 5.10	500 mg = 6.75
Dexamethasone		0.5 mg × 3 = 3.99	8 mg × 3 capsules = 3.74
Melphalan		2 mg = 9.64	2 mg = 78.03
Prednisone		1 mg × 30 = 1.12	2 mg × 30 = 24.05
Vincristine		1 mg/ mL × 5 = 41.56	0.4 mg = 6.8
Cisplatin		50 mg = 4.59	10 mg × 1 = 3.98
Etoposide		100 mg/5 mL = 4.08	100 mg × 1 = 7.10
Bisphosphonates			
Aredia	15 mg/ mL = 29.83	15 mg = 15.32	3 mg/ mL × 5 mL = 15.78
Bondronat	50 mg × 28 = 183.69	6 mg/6 mL = 286.40	50 mg × 28 cpr = 365.60
Clastoban	400 mg × 30 capsules = 34.96	400 mg × 60 capsules = 115.69	400 mg × 10 capsules = 23.79
Lytos		520 mg × 30 capsules = 113.48	400 mg × 10 capsules = 23.79
Pamidronate generic	3 mg × 5 = 13.33	3 mg/ mL × 30 mL = 194.30	3 mg/ mL × 5 mL = 15.78
Zometa	4 mg = 174.17	4 mg/100 mL = 255.72	4 mg = 226.36
G-CSF			
Filgrastim biosimilar	30 MUI = 50.15	30 MUI = 99.87	30 MUI = 63.65
Granocyte	33.6 MUI = 62.54	34 MUI = 92.65	33.6 MUI = 84.88

Neulasta	6 mg = 686.38	6 mg = 979.36	6 mg = 908
Neupogen	30 MUI = 52.70	30 MUI = 99.87	30 MUI = 63.17
ESA			
Aranesp	100 mcg = 146.81	100 mcg = 146.53	100 mcg = 201.26
Eprex	1000 UI = 5.53	2000 UI = 17.87	1000 UI = 15.52
Neorecormon	2000 UI = 14.03	1000 UI = 10.78	2000 UI = 21.03
Epoetin biosimilar	1000 UI = 5.66	1000 UI/0.5 mL = 6.74	1000 UI × 6 = 51.12
Anti-infective (oral)			
Quinolones second generation		400 mg × 3 = 12.09	400 mg × 20 = 4.59
First-generation cephalosporins		250 mg × 12 = 4.50	1000 mg = 1.72*
Second-generation cephalosporins		500 mg × 8 = 8.30	1000 mg = 3.77*
Third-generation cephalosporins		1000 mg/10 mL = 6.82	1000 mg = 4.51*
Fourth-generation cephalosporins		1000 mg = 8.44	1000 mg = 7.76*
Targocid	200 mg = 3.93	200 mg = 26.15	200 mg = 37.83*
Penicillin M	250 mg × 25 = 4.75	500 mg × 16 = 4.27	1000 mg × 12 = 9.72
Vancomycin	125 mg × 28 = 88.31	125 mg = 1.53	250 mg × 4 = 16.54
Amoxycillin	250 mg × 21 = 3.38	1000 mg × 14 = 4.46	1000 mg × 12 = 2.97
Amoxycillin + clavulanic acid		1 g + 125 mg × 12 = 8.23	875 + 125 mg × 12 = 7.18
Aminoglycoside		160 mg = 2.96	100 mg = 3.60*
Co-trimoxazole	960 mg × 28 = 6.57	800 mg/160 mg × 10 = 1.69	960 mg × 16 = 3.38
Anti-infective (IV)			
First generation cephalosporins IV		1000 mg/3 mL = 3.54	1000 mg = 1.72
Second generation cephalosporins IV		1000 mg = 2.32	1000 mg = 3.77
Third generation cephalosporins IV		1000 mg = 8.10	1000 mg = 4.51
Fourth generation cephalosporins IV		1000 mg = 8.44	1000 mg = 7.76
Targocid IV	200 mg = 3.93	200 mg = 26.15	200 mg = 37.83
Penicillin M IV	500 mg = 0.55	1 MUI × 25 = 27.21	1000 mg = 2.73
Vancomycin IV	500 mg = 6.25	500 mg = 2.55	1000 mg = 9.29
Amoxycillin IV	500 mg = 0.55	1000 mg = 2.32	1000 mg × 100 = 40.98
Amoxycillin + clavulanic acid IV		2000 mg × 10 = 26.51	1000 + 200 mg = 2.84

Aminoglycoside IV	80 mg × 1 = 4.00	80 mg × 1 = 1.91	100 mg = 3.60
Anti-fungal (oral)			
Sporanox	100 mg × 4 = 3.67	100 mg × 30 = 35.38	100 mg × 8 = 6.82
Triflucan	50 mg × 7 = 16.61	100 mg × 7 = 20.95	100 mg × 10 = 24.21
VFEND/Voriconazole generic	200 mg × 28 = 1102.74	200 mg = 38.59	200 mg × 28 = 1586.71
Noxafil	100 mg × 24 = 596.96	100 mg = 31.15	100 mg × 24 = 1005.89
Fluconazole generic	50 mg × 7 = 1.02	50 mg × 7 = 18.19	100 mg × 10 = 24.21
Itraconazole generic	100 mg × 15 = 4.57	100 mg × 30 = 35.38	100 mg × 8 = 6.82
Anti-fungal (IV)			
Fungizone	50 mg = 3.88	50 mg = 7.15	50 mg = 5.23
Abelcet	100 mg = 77.50	5 mg × 20 = 132.73	100 mg × 10 = 861.56
Ambisome	80 mg = 82.19	50 mg = 155.19	50 mg × 10 = 3262.20
Sporanox IV	10 mg × 25 = 79.71	10 mg/ mL = 87.16	250 mg = 112.81
Triflucan	200 mg = 29.28	2 mg/ mL × 100 mL = 18.38	100 mg = 5.50
VFEND IV	200 mg = 77.14	200 mg = 136.12	200 mg = 112.40
Pain (oral)			
Paracetamol	500 mg × 30 = 1.19	1000 mg × 8 = 1.08	1000 mg × 16 = 6.40
Nefopam		20 mg/2 mL = 2.89	
NSAID (unspecified)		0.35 mL × 20 = 3.14	100 mg × 20 = 4.36
Paracetamol + Codeine	500 mg + 8 mg × 30 = 1.19	500 mg + 30 mg × 16 = 1.71	500 mg + 30 mg × 16 = 2.87
Dihydrocodeine		60 mg × 20 = 5.46	15 g (10.25 mg/ mL) = 4.18
Tramadol	50 mg × 30 = 2.29	50 mg × 30 = 4.08	100 mg × 10 = 3.85
Tramadol + Paracetamol		37.5 mg + 325 mg × 20 = 2.50	37.5 mg + 325 mg × 20 = 11.70
Morphine hydrochloride	10 mg × 100 = 24.09	10 mg/ mL × 10 = 9.26	
Morphine sulphate	30 mg = 0.72	2 mg/ mL = 8.01	100 mg × 16 = 20.77
Hydromorphone	1.3 mg × 56 = 8.82	16 mg × 14 = 43.16	16 mg × 14 = 48.34
OxyContin	5 mg × 28 = 12.52	5 mg × 28 = 7.59	10 mg × 28 = 14.23
Oxycodone generic	10 mg × 56 = 22.86	10 mg × 28 = 7.11	10 mg × 28 = 7.82
Pain (patch)			
Durogesic	12 mcg × 5 = 12.59	12 mcg × 5 = 13.15	12 mcg × 3 = 6.68

Fentanyl generic	12 mcg × 5 = 12.59	12 mcg × 5 = 13.15	12 mcg × 3 = 4.88
Pain (SC)			
Morphine hydrochloride	10 mcg/h × 4 = 0.97	10 mg/ mL × 10 = 9.26	10 mg = 1.45
Oxecta	10 mcg/h × 4 = 0.97		
Oxycodone hydrochloride	10 mcg/h × 4 = 0.97		
Anti-viral (oral)			
Zovirax	200 mg × 25 = 2.85	200 mg × 25 = 12.26	200 mg × 25 = 16.44
Cymevan/ganciclovir generic	500 mg = 29.77	250 mg × 84 = 356..77	500 mg = 26.21
Acylovir generic	200 mg × 25 = 1.77	200 mg × 25 = 12.26	200 mg × 25 = 10.26
Anti-viral (IV)			
Valcyte	450 mg × 60 = 1081.46	450 mg × 60 = 1440.89	450 mg × 60 = 1083.31
Valganciclovir generic	500 mg × 10 = 3.76	450 mg × 60 = 1440.89	450 mg × 60 = 1083.31
Other			
Tamiflu		30 mg × 10 = 11.60	30 mg × 10 = 17.30
Tazocin			4 g × 12 = 147.83
Carbapenem		500 mg = 9.17	500 mg × 10 = 64.77*
Zelitrex		500 mg × 42 = 49.80	500 mg × 42 = 44.17
Zyvoxid Dalacine		150 mg × 12 = 3.04	600 mg × 10 = 831.14
Lyrica	150 mg × 56 = 64.40	100 mg × 84 = 41.93	150 mg × 14 = 18.95
Aspegic		1 000 mg × 20 = 3.35	75 mg × 30 = 2.11
Bactrim		800 mg × 10 = 2.00	800 +160 mg × 16 = 3.38
Dalteparin	10000 UI × 10 = 5.65	10 000 UI × 5 = 40.75	10000 UI × 4 = 33.48
Clexane		100 mg x2 = 24.93	10000 UI × 10 = 59.87
Warfarin	5 mg × 28 = 1.08	10 mg × 25 = 3.98	5 mg × 30 = 1.97
Pradaxa	110 mg × 10 = 10.98	110 mg × 10 = 13.28	110 mg × 10 = 16.66
Esomeprazole (nexium)	20 mg × 28 = 18.50	20 mg × 7 = 6.46	10 mg × 28 = 16.75
Kardegic		160 mg × 30 = 2.08	75 mg × 30 = 2.11
HBPM		100 mg × 2 = 24.93	160 mg + 12.25 mg × 28 = 6.14
Isosorbide dinitrate		40 mg × 60 = 4.33	40 mg × 50 = 4.45
Micardis		40 mg × 28 = 16.85	20 mg × 28 = 5.34

Renagel		400 mg × 360 = 151.94	800 mg × 180 = 85.47
Gabapentin, neurontin		100 mg × 90 = 8.50	100 mg × 50 = 5.45
Oxycodone naloxone			10 mg + 5 mg × 28 = 24.08
Pregabalin		100 mg × 84 = 41.93	150 mg × 14 = 18.95
Enoxparin	20 mg = 2.27		
Innohep	2500 UE = 1.98		

ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte-colony stimulating factor; IV, intravenous; SC, subcutaneous; universal equivalents.

Supplementary Table 3. Non-drug unit costs by country.

Country	UK (£)	France (€)	Italy (€)
Additional costs			
Spinal cord compression	1355.00		19 545.00
Hip fracture	7169.89		1985.00
Vertebral fracture	2755.32		4935.67
Other fracture	2234.48		3649.00
Tracheotomy	3141.00		5516.98
Transcatheter aortic valve implantation	16 650.00		24 675.00
Surgery after laryngeal compression	2267.00		10 658.00
Drug administration		1535.82	
Surgery		11 736.76	
Toxicity management		6171.28	
Palliative care		4094.75	
Stem cell transplant		18 924.96	
Fracture		4687.87	
Transfusion		621.65	
Routine tests		644.09	
Poor overall condition		6171.28	
Renal Failure		6484.15	
Pneumonia		4242.22	
Radiotherapy		644.09	
Pain management		644.09	
Other		6171.28	
Consultations			
Hematologist	3.00	25.70	20.66
Oncologist	1.18	25.70	20.66
Onco-hematologist	1.18	25.70	20.66
Surgeon	44.72	25.70	20.66
Organ specialist	30.50	25.70	20.66

Nurse	4.85	3.15	4.30
GP	5.60	23	0.00
Re-education physician / Orthopedic	19.55	25.70	20.66
ER physician	1.18		20.66
Anesthetist	26.20	25.70	20.66
Geriatrician	26.20	25.70	20.66
Infectious diseases	14.91	25.70	20.66
Radiologist	7.35	25.70	20.66
Pain therapy	12.85	25.70	20.66
Palliative care	26.20	25.70	20.66
Laboratory test			
Routine blood count	3.00	7.83	3.17
Biochemistry	1.18	20.25	12.32
Liver function test	1.18	21.33	13.60
Immunoglobulin	44.72	16.29	4.99
Paraprotein measurements	30.50		
Protein electrophoresis	4.85	18.90	4.23
Serum beta 2 microglobulin	5.60	9.45	5.30
Serum immunofixation	19.55	48.60	20.88
Creatinine clearance	1.18	8.10	1.60
Serum free light chains	26.20		10.60
24 hr total urine protein	26.20	6.75	3.52
Urine protein electrophoresis/light chains	14.91	14.85	4.23
Urine immunofixation	7.35	48.60	20.88
Bence Jones 24 h	12.85	48.60	1.13
C reactive protein	4.75	2.70	3.87
Immunophenotyping	7.77	145.80	153.96
Karyotype	10.49	216.00	134.09
Sputum culture	6.84	33.75	6.35
NT-proBNP	3.00	22.68	12.55
D dimer	3.00	12.15	7.65

Scan			
Skeletal survey by x-ray	147.00	159.60	90.38
Skeletal survey by x-ray (individual site)	80.00	23.94	18.71
MRI	235.00	62.00	158.63
PET scan	147.00	89.54	1 071.65
Radiotherapy	234.00	137.78	54.09
Bone densitometry	70.00	39.96	37.44
Bone marrow aspirate	10.00	37.01	48.86
Bone marrow trephine biopsy	10.00	37.01	48.86
Bacterial investigation	7.00	17.55	10.31
Lactic dehydrogenase	3.00	1.89	1.13
Calcium	8.00	1.89	1.13
Magnesium	8.00	1.89	1.55
Bone scintigraphy	766.00	210.05	83.10
Biopsy (other)	10.00		33.78
CT scan	129.00	50.54	94.64
Ultrasound/echography	90.00	87.87	60.43

CT, computed tomography; ER, emergency room; GP, general practitioner; MRI, magnetic resonance imaging; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PET, positron emission tomography.

Supplementary Table 4. Physician characteristics.

	UK (n=56)	France (n=76)	Italy (n=57)
Specialty			
Hematologists	40 (71)	46 (61)	52 (91)
Onco-hematologists	1 (2)	25 (33)	2 (4)
Oncologists	15 (27)	3 (4)	3 (5)
Internists	-	2 (3)	-
Hospital type			
Non-university hospitals	9 (16)	32 (42)	28 (50)
University hospitals	40 (71)	28 (37)	25 (43)
Private hospitals	-	8 (11)	-
Cancer centers	7 (13)	8 (11)	4 (7)

Values are n (%).

Supplementary Table 5. Total costs (€) across treatment lines (2L–5L+), by treatment type and country.

	Lenalidomide-based	Bortezomib-based	Pomalidomide-based	Bendamustine-based
UK				
Mean	54 346	23 994	78 594	18 810
Median	40 235	23 098	60 791	12 608
France				
Mean	44 248	35 344	64 876	14 306
Median	40 435	34 722	49 032	12 354
Italy				
Mean	64 369	26 628	–	10 001
Median	43 671	21 987	–	7 451

An exchange rate of €1 = £0.7178 was used (1 June 2015).
2L–5L+, second-line to fifth-line treatment line and beyond.

Supplementary Table 6. Total costs (€) according to patient ECOG performance status

	UK			France			Italy		
Period duration by treatment (months)	ECOG 0	ECOG 1	ECOG 2+	ECOG 0	ECOG 1	ECOG 2+	ECOG 0	ECOG 1	ECOG 2+
Active treatment									
Mean	69 508.59	45 791.12	20 635.59	45 787.97	38 797.64	34 051.75	36 662.88	35 198.54	29 799.8
Median	51 620.43	34 515.79	20 142.49	36 722.00	34 419.00	32 130.50	23 129.50	23 859.00	16 943.0
Off treatment									
Mean	981.68	892.23	127.19	640.50	112.50	649.00	753.62	1 006.30	3 454.0
Median	321.09	–	–	1 791.63	1 124.56	2 054.53	263.50	229.00	
Post-progression									
Mean	2 173.79	824.13	475.03	678.56	1 243.39	3 116.00	274.5	367.50	1 091.0
Median	308.58	175.14	50.74	302.50	273.00	-	1 054.32	1 253.22	2 422.7

ECOG, Eastern Cooperative Oncology Group

Supplementary Table 7. Total costs (€) according to patient SCT status

Period duration by treatment (months)	UK		France		Italy	
	SCT	No SCT	SCT	No SCT	SCT	No SCT
Active treatment						
Mean	47 385.78	47 860.23	43 188.50	37 645.85	36 429.06	33 976.04
Median	34 082.80	34 820.89	36 373.00	34 603.00	24 388.50	21 580.00
Off treatment						
Mean	965.93	873.82	1306.75	1168.14	926.33	1345.96
Median	407.27	–	114.00	158.00	371.00	165.00
Post-progression						
Mean	1740.20	755.24	1205.86	1299.31	1368.87	1318.14
Median	643.57	123.71	270.00	281.00	432.00	350.50

SCT, stem cell transplant.