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Multiple Myeloma Disease Coverage

- Forecast
- Treatment
- Epidemiology
- Marketed Drugs
- Pipeline

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Multiple Myeloma

Forecast Extract

Catalyst

Modest market growth will be driven by label expansions and new launches, but will be moderated by genericization of Revlimid and Velcade.

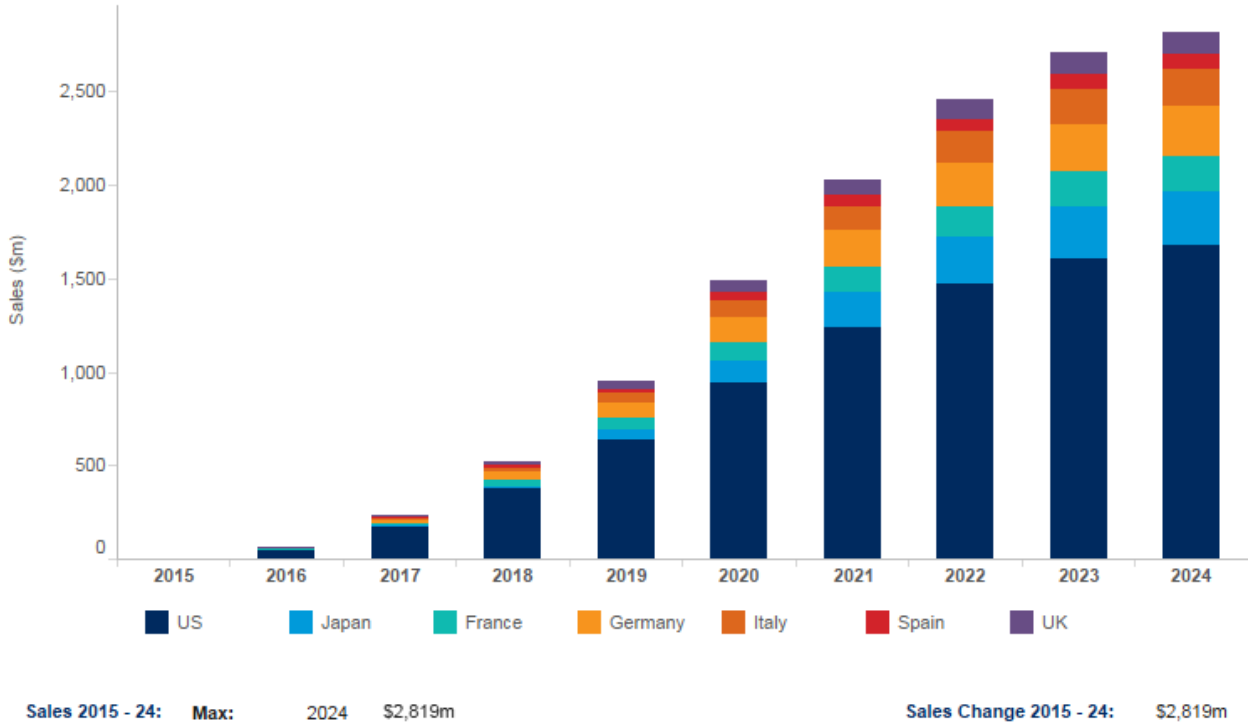
7 April 2016

Elsa Willebrand

Datamonitor Healthcare forecasts that the extended indications for these drugs will lead to considerable uptake across the treatment algorithm, which will strongly contribute to the total sales of MM drugs.

The figure and table below show Datamonitor Healthcare's sales forecast of Darzalex, Empliciti, and Ninlaro in the US, Japan, and five major EU markets during 2015–24.

Figure 5: Combined sales of Darzalex, Empliciti, and Ninlaro in the US, Japan, and five major EU markets, by country, 2015–24



Sales 2015 - 24: **Max:** 2024 $2,819m **Sales Change 2015 - 24:** $2,819m

Source: Datamonitor Healthcare

VELCADE (BORTEZOMIB)

Forecast assumptions

Datamonitor Healthcare makes the following assumptions in its forecast of Velcade (bortezomib; Takeda/Johnson & Johnson) in the treatment of multiple myeloma (MM):

- In the US and EU, Velcade is approved for the treatment of MM in all treatment settings (Velcade prescribing information, 2015; Velcade product information, 2016). In Japan, Velcade is approved for the treatment of relapsed/refractory MM (Takeda press release, 2010). In this forecast, Datamonitor Healthcare has not distinguished between intravenous and subcutaneous use of Velcade.
- Datamonitor Healthcare assumes the dosing schedule of Velcade to be 2.34mg administered once or twice weekly in the first line, and once weekly as maintenance therapy. The duration of treatment is based on the prescribing information in the US and EU, and on what has been specified in the VISTA, IFM 2005-01, and MMY-3010 trials (ClinicalTrials.gov identifiers: NCT00111319, NCT00200681, and NCT00103506 respectively; Velcade prescribing information, 2015; Velcade product information, 2016).
- Velcade's anticipated patent expiries in Q2 2017 in the US, in Q1 2019 in Japan, and in Q2 2019 in the EU will result in a considerable loss of market share to generic bortezomib.
- Datamonitor Healthcare forecasts that Velcade will lose further market share to Kyprolis (carfilzomib; Amgen/Ono Pharmaceutical), which drastically improved progression-free survival when compared head-to-head with Velcade in second-line patients in the ENDEAVOR trial (ClinicalTrials.gov identifier: NCT01568866; Dimopoulos et al., 2015). The ongoing ECOG trial (ClinicalTrials.gov identifier: NCT01863550) is evaluating Kyprolis head-to-head with Velcade in the first-line setting. Datamonitor Healthcare expects a favorable outcome for Kyprolis, leading to a label expansion, with a substantial loss of revenue for Velcade as a result.
- Takeda's oral second-generation proteasome inhibitor Ninlaro (ixazomib) will capture considerable market share from Velcade in the first-line, maintenance, and second-line settings following anticipated label expansions.
- Please view the accompanying interactive dashboard and Excel deliverable for further details on Datamonitor Healthcare's forecast of Velcade.
- For further details on Datamonitor Healthcare's assessment of Velcade and its competitive positioning, please refer to the full drug profile in Marketed Drugs: Multiple Myeloma.

Velcade forecast, 2015–24

The figure and table below show Datamonitor Healthcare's forecast of Velcade in MM, by country, over 2015–24.

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Multiple Myeloma

Treatment Extract

Catalyst

Velcade and Revlimid dominate early treatment settings but are replaced by newer drugs as patients relapse and become refractory to treatment.

6 April 2016
Elsa Willebrand

PATIENT SEGMENTATION

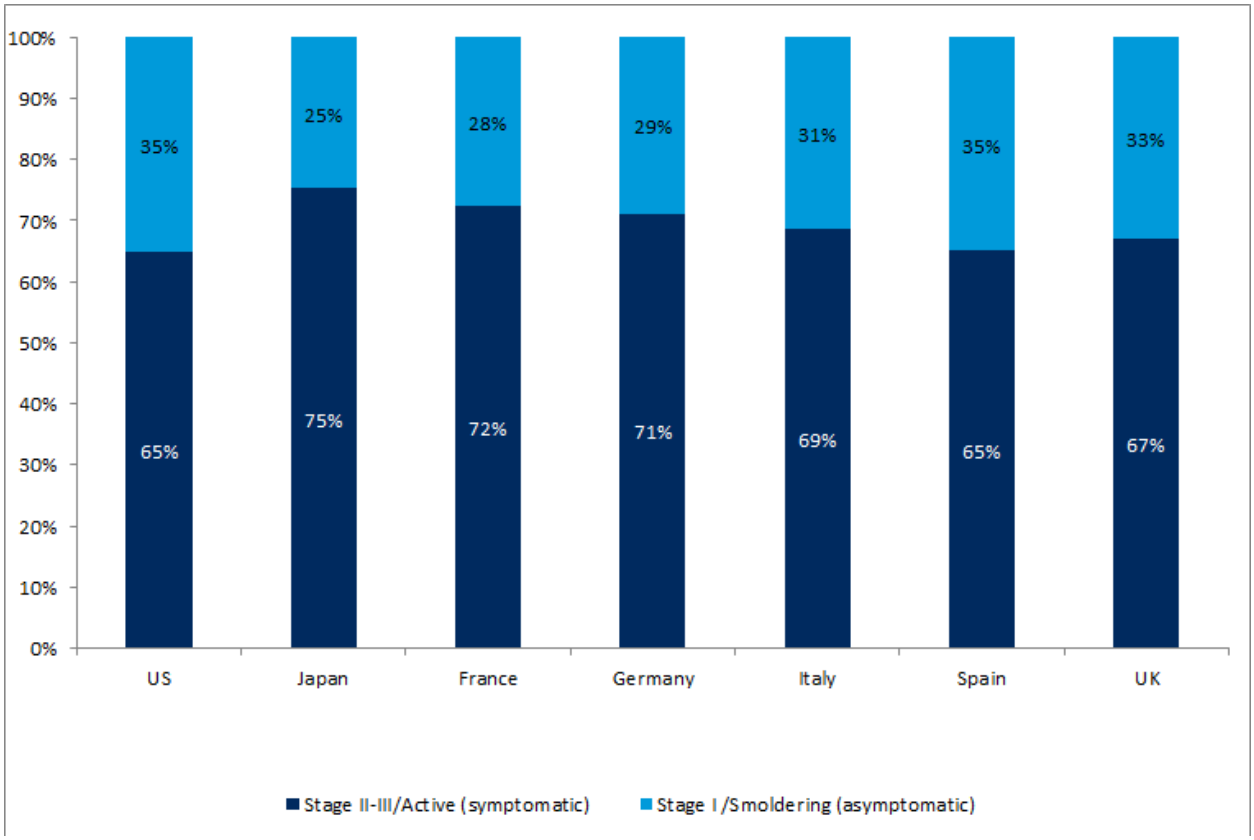
Stage distribution

Multiple myeloma (MM) can be classified according to several different staging systems, including the Durie-Salmon staging, the International Staging System (ISS), and the revised ISS. Major guidelines still recommend treatment depending on whether the disease is classified as smoldering MM (SMM) or active MM. In this analysis, Datamonitor Healthcare has assumed that active MM corresponds to Durie-Salmon Stages II–III and that SMM corresponds to Durie-Salmon Stage I.

Smoldering multiple myeloma

Datamonitor Healthcare's survey indicated that the majority of MM patients across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) present with active (Stage II–III) MM. The figure below shows the estimated proportion of patients with SMM (asymptomatic) versus active MM (symptomatic).

Figure 1: Patients diagnosed with symptomatic and asymptomatic multiple myeloma, by country (%)



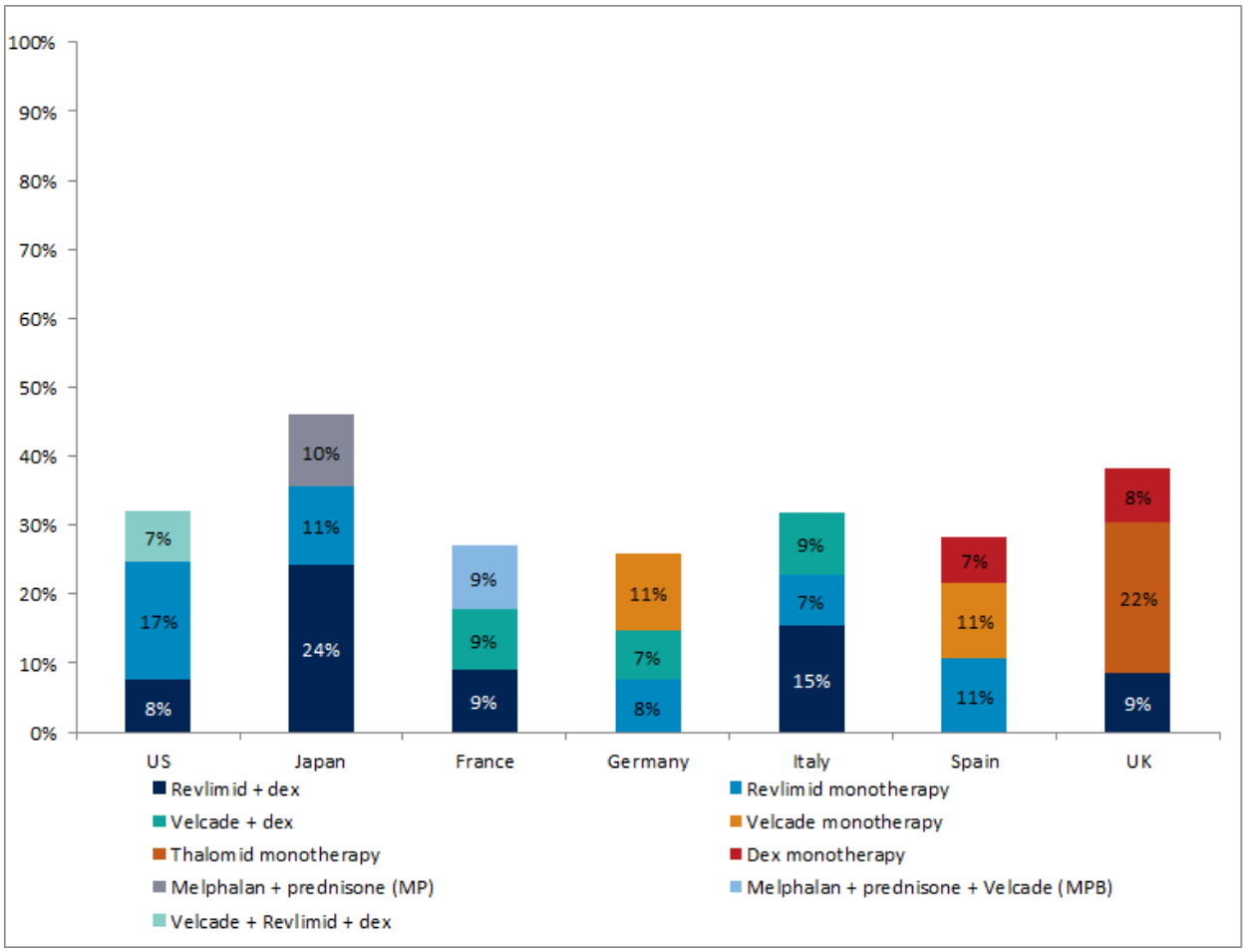
Source: Datamonitor Healthcare's proprietary multiple myeloma survey, December 2015

SMM is a heterogeneous disease stage in-between monoclonal gammopathy of undetermined significance and active MM, defined with abnormal levels of M-protein but with a lack of organ

The regimens given as maintenance treatment after induction therapy are similar to those given after SCT. Maintenance therapies for patients not eligible for SCT are dominated by monotherapies or drugs used in combination with dexamethasone. As observed in the maintenance setting following SCT, there is high off-label use of Revlimid in most regions.

The figure below shows the top three chemotherapy regimens used in maintenance therapy following first-line treatment of active (Stage II–III) MM patients that are not eligible for SCT across the US, Japan, and five major EU markets in 2015.

Figure 15: Top three regimens used for maintenance after induction therapy in multiple myeloma patients not eligible for SCT, by country



Source: Datamonitor Healthcare's proprietary multiple myeloma survey, December 2015

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SECOND-LINE THERAPY

SECOND-LINE THERAPY FOR PATIENTS NOT ELIGIBLE FOR SCT IS TYPICALLY LESS AGGRESSIVE THAN THAT GIVEN TO PATIENTS AFTER SCT

The second-line prescribing trends for RRMM patients that have not received an SCT are relatively similar to those in patients that have received an SCT. However, this patient group typically receives

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Multiple Myeloma

Epidemiology Extract

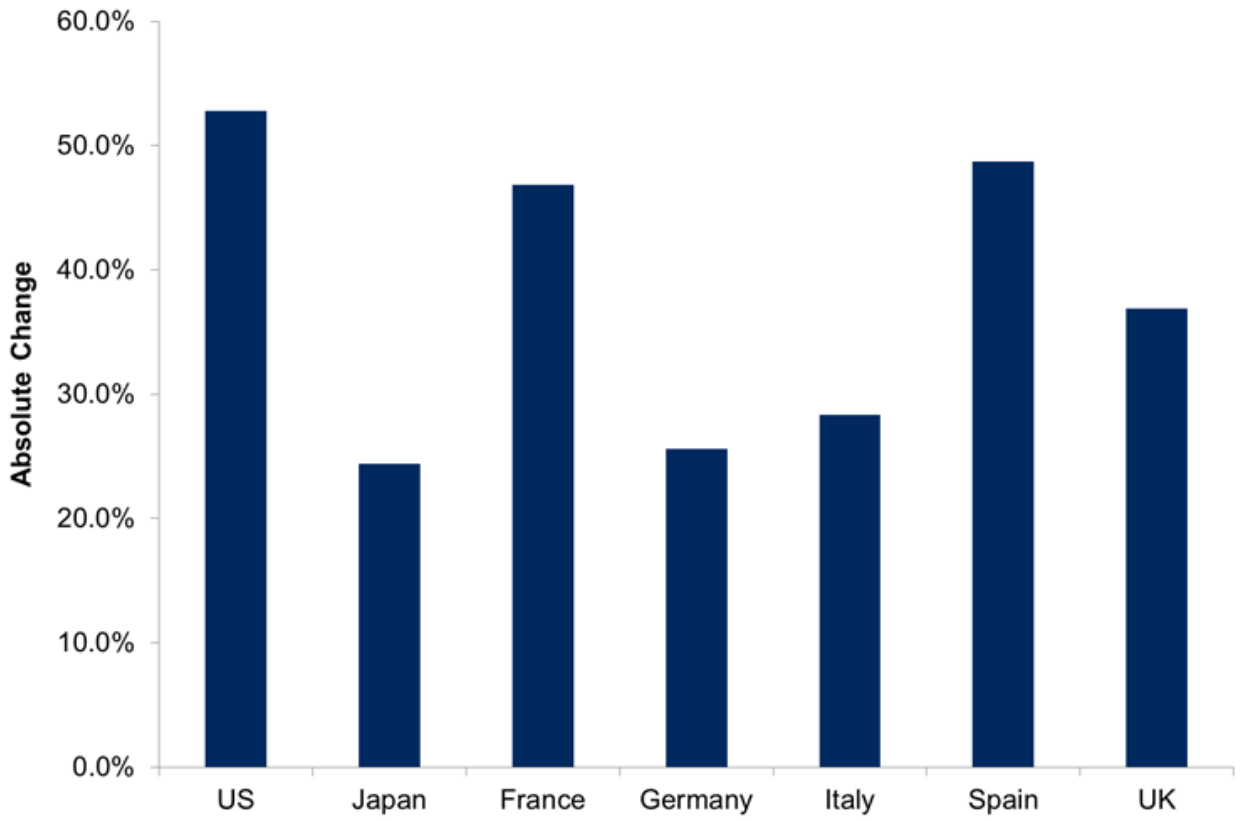
25 April 2016

Amy Brenner

will increase the number of people at risk of MM because MM generally affects elderly individuals.

- Based on secular trends in MM incidence, Datamonitor Healthcare predicts that incidence rates will increase over the forecast period. Growth in the incident MM population is also attributable to this factor.
- The US is expected to see the greatest increase in the number of incident cases of MM during the forecast period, with an absolute increase of 52.8%, which equates to 11,950 additional incident cases. France and Spain are predicted to experience similar levels of growth, with an almost 50% increase in the number of incident cases of MM during 2014–34 (46.9% and 48.5% increase, respectively).
- Meanwhile, Datamonitor Healthcare estimates that in Japan, Germany, and Italy, the incident MM population will undergo more modest increases of 24.3%, 25.7%, and 28.4%, respectively. This reflects a smaller expected increase in incidence rates in these countries.

Figure 3: Absolute growth in incident cases of multiple myeloma in the US, Japan, and five major EU markets, by country, 2014–34



Source: Datamonitor Healthcare; Ferlay et al., 2014; National Cancer Institute, 2015; Robert Koch Institute, 2015; United Nations, 2013

AGE- AND GENDER-SPECIFIC INCIDENT CASES OF MULTIPLE MYELOMA

WHILE MULTIPLE MYELOMA IS MOST COMMON AT OLDER AGES, THE AGE DISTRIBUTION VARIES

GEOGRAPHICALLY

- Datamonitor Healthcare estimates that in 2014, 82.7% of incident MM cases in the US, Japan, and five major EU markets were diagnosed in individuals aged 60 years or older (43,120 cases), and 56.7% were diagnosed in those aged 70 years or older (29,570 cases).
- Overall, the 70–79 year-old age group comprised the greatest number of incident cases of MM in 2014 (16,130 cases; 30.9%). On a country basis, this was true for Germany, Italy, Spain, and the UK, whereas in Japan the 80+ age group comprised a higher proportion of cases, which is likely due to differences in the age structure of the populations.
- In the US in 2014, incident cases of MM had a younger age distribution, with a higher proportion of cases aged under 70 years old and a smaller proportion aged 70 or older compared to the other countries analyzed. Specifically, 50.9% (11,510 cases) of incident cases in the US were in those aged under 70, compared to 29.3-–40.5% in the other countries. This may be due to the US's younger age structure or geographic variation in risk factor distribution, resulting in an increased risk of MM at younger ages compared to the other countries.
- In contrast, incident cases of MM in Japan had the oldest age distribution in 2014, with 70.5% of incident cases aged 70 or older compared to 59.9–61.7% in the five major EU markets. This is a consequence of Japan's age structure, since 18.3% of the population was aged 70 years or older in 2014 (United Nations, 2013).

Table 8: Age-specific incident cases of multiple myeloma in the US, Japan, and five major EU markets, by country, 2014

Age group (years)	US	Japan	France	Germany	Italy	Spain	UK	5EU	Total
40–49	1,230	90	140	260	230	100	150	880	2,200
50–59	3,670	280	610	770	700	330	490	2,900	6,850
60–69	6,610	1,040	1,210	1,570	1,330	680	1,100	5,900	13,550
70–79	6,400	1,570	1,510	2,610	1,820	840	1,390	8,160	16,130
80+	4,730	1,830	1,530	1,570	1,700	800	1,290	6,880	13,440
Total	22,630	4,820	5,010	6,780	5,780	2,740	4,410	24,720	52,170

Note: totals may not sum due to rounding.

5EU = five major EU markets (France, Germany, Italy, Spain, and the UK)

Source: Datamonitor Healthcare; Ferlay et al., 2014; National Cancer Institute, 2015; Robert Koch Institute, 2015; United Nations, 2013

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Multiple Myeloma

Marketed Drugs Extract

12 February 2016
Elsa Willebrand

Table 6: Empliciti drug profile

Molecule	elotuzumab
Mechanism of action	Targets SLAMF7
Originator	Abbott
Marketing company	Bristol-Myers Squibb, AbbVie
Approved indication	Multiple myeloma treated with one to three prior lines of therapy
Contraindications	None
Formulation	Intravenous
Pricing strategy	$10,890 per average treatment cycle
Dosing frequency	10mg/kg once weekly for the first two 28-day cycles, and once every two weeks for the following cycles
First approval date for multiple myeloma	November 2015 (US)
Primary patent expiry	Q2 2024 (US); Q4 2024 (Japan and 5EU)
Geographic availability	US
Alternative names	HuLuc63, BMS-901608
2014 global total brand sales	n/a
5EU = five major EU markets (France, Germany, Italy, Spain, and the UK); SLAMF7 = signaling lymphocytic activation molecule F7	

Source: BioMedTracker, Copyright 2015, reprinted with permission; Medtrack, November, 2015, Copyright Informa UK; Pharmaprojects®, 2015; Citeline; Scrip Intelligence, 2015

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DEVELOPMENT OVERVIEW

Empliciti was developed by Facet Biotech, which was part of PDL BioPharma before being spun off. Facet Biotech was later acquired by Abbott, of which AbbVie was a part until a separation occurred in 2013. Bristol-Myers Squibb and PDL BioPharma announced an agreement in August 2008 giving Bristol-Myers Squibb development and marketing rights to Empliciti (BioMedTracker, Copyright 2015, reprinted with permission).

Farydak is associated with significant toxicity which will have a negative effect on uptake

Patients treated with Farydak experience a considerable level of adverse events, which is likely to strongly affect uptake of the drug and prevent expansion to earlier lines of therapy. Commenting on Farydak's initial application for approval, the FDA's advisory committee stated it did not consider that the benefits of improved PFS outweighed the risks of on-treatment deaths and withdrawals due to adverse events (Pink Sheet, 2014; Copyright Informa UK). In the PANORAMA-1 trial, 60% of patients experienced serious adverse events in the Farydak treatment arm compared to 42% in the control arm. Grade 3/4 diarrhea occurred in 25% of the patients treated with Farydak compared to 8% of patients receiving Velcade and dexamethasone only, while 25% of patients receiving Farydak experienced grade 3/4 fatigue compared to 12% in the control arm. Additionally, 36% of patients treated with the Farydak-containing regimen discontinued treatment due to adverse events, compared to 20% in the control arm (Farydak prescribing information, 2015; San-Miguel et al., 2014).

Use of the HDAC inhibitor Zolinza (vorinostat; Merck & Co) in the treatment of patients with cutaneous T-cell lymphoma has also been associated with considerable tolerability issues stemming from the drug's gastrointestinal toxicity including nausea, vomiting, and diarrhea (Zolinza prescribing information, 2014). Key opinion leaders interviewed by Datamonitor Healthcare cited such tolerability issues as a cause for concern with the use of HDAC inhibitors.

"I think that as we learn more about HDAC inhibitors they may have a role [in multiple myeloma]. In terms of their use in lymphoma patients, it has been limited by side effects. The patients treated with HDAC inhibitors have had some terrible nausea and vomiting and that has been difficult for them to tolerate, but it may be an issue of dose and schedule that needs to be refined."

US key opinion leader

Farydak has a boxed warning about increased risks of severe diarrhea, severe and fatal cardiac ischemic events, severe arrhythmias, and changes in electrocardiogram, while a Risk Evaluation and Mitigation Strategy (REMS) is also in place to help minimize these toxicities through communication and information to healthcare professionals (FDA news release, 2015). The toxicity associated with Farydak will affect uptake of the drug, and is likely to keep it in the third-line setting.

Farydak looks set to be an option for patients who are not responding to other available drugs

Farydak demonstrates a less favorable profile compared to competitors, but will see some uptake in the third-line setting. In the PANORAMA-1 trial, Farydak failed to demonstrate efficacy that could outweigh the adverse events observed, but when a more heavily pretreated subgroup was analyzed, the benefits of the treatment were more pronounced (Farydak prescribing information, 2015). Patients refractory to proteasome inhibitors and IMiDs will benefit from a drug with a new mechanism of action, and Farydak is likely to experience uptake in third-line therapy for patients who are refractory to most other available treatments.

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Multiple Myeloma

Pipeline Extract

Catalyst

Keytruda has an extensive development program and promising early-phase data in multiple myeloma.

10 February 2016

Elsa Willebrand

CLINICAL TRIAL DESIGN

Clinical trials are imperative to determine the efficacy and safety of all developmental products, and they are compulsory for gaining marketing approval. Factors such as dosing schedules, patient selection, patient numbers, and trial duration need to be established prior to trial initiation in order to gain statistically meaningful results. The aim for most companies is to strike a balance between designing clinical trials to optimize the chances of approval while simultaneously conducting the trial with economic prudence.

Clinical trials

CLINICAL RESPONSE IS BASED ON SEVERAL DIFFERENT PARAMETERS

To evaluate response to multiple myeloma (MM) treatment, several different criteria are assessed. Response rates are divided into different categories such as complete response, partial response, and minimal response, defined by criteria which have been characterized by several different groups. One of the most commonly used sets of criteria was published by the European Group for Blood and Marrow Transplantation (EBMT) in 1998, and is based on the levels of bone lesions, M protein, plasma cells in bone marrow, light-chain urine excretion, and soft tissue plasmacytomas (Bladé et al., 1998).

In 2006, the International Myeloma Working Group (IMWG) published criteria for MM, and these are currently considered to be standard, although the EBMT criteria are still in use. The IMWG criteria are similar to those developed by the EBMT, but include the addition of the categories of stringent complete response and very good partial response, as well as clarifications and the addition of response criteria for interpreting the serum free light-chain assay (Durie et al., 2006; Kyle and Rajkumar, 2009).

Commonly used clinical trial endpoints for multiple myeloma

PROGRESSION-FREE SURVIVAL IS THE STANDARD PRIMARY ENDPOINT

Progression-free survival (PFS) is the most commonly used primary endpoint for Phase III trials supporting US Food and Drug Administration (FDA) approvals. It is defined as the time from the start of treatment to disease progression or death from any cause. The IMWG definition of progression to disease requires one or more of the following:

- increase of greater than or equal to 25% in serum or urine M-component
- bone marrow plasma cell percentage of at least 10%
- definite development of bone lesions or soft tissue plasmacytomas
- definite increase in existing bone lesions or soft tissue plasmacytomas
- development of hypercalcemia that can be attributed to the plasma cell malignancy
- a change in the free light-chain ratio (only for patients with no measurable M-components).

PFS is the IMWG's recommended endpoint for trials (Durie et al., 2006).

LATE STAGE DRUGS

Aplidin : Multiple myeloma

PRODUCT PROFILE

Analyst Outlook

Aplidin (plitidepsin) is a cyclic depsipeptide antitumor agent developed by the Spanish company PharmaMar. In 2004, Aplidin gained orphan drug designation in the US and EU for the treatment of multiple myeloma (MM), and it is currently in Phase III development for the disease. PharmaMar is positioning it as a fourth-line therapy for heavily pretreated MM patients in combination with dexamethasone. Targeting fourth-line therapy will significantly limit the potential share for Aplidin in the MM market. Datamonitor Healthcare also believes that Aplidin will face strong competition from existing therapies with proven efficacy in heavily pretreated patient groups.

Drug Overview

Aplidin is an intravenous, marine-originated cyclic depsipeptide antitumor agent. The drug, which is currently synthesized chemically, was originally isolated from the marine tunicate Aplidium albicans (Cuadrado et al., 2003; PharmaMar, 2014). Aplidin's exact mechanism of action is not fully understood, but it is believed to induce cytotoxicity through several pathways. It has been shown to inhibit the cancer-associated Eukaryotic elongation factor 12 (eEF1A2) (PharmaMar press release, 2015; Lee and Surh, 2009), as well as disrupting the glutathione homeostasis and activating mitogen-activated protein kinases, leading to caspase-dependent apoptosis (García-Fernández et al., 2002; González-Santiago et al., 2006). Aplidin has also been shown to block cell division in the G1/G2 phase, and inhibit the secretion of vascular endothelial growth factor (Biscardi et al., 2005; Erba et al., 2002).