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SPOTLIGHT ON... MULTIPLE MYELOMA

A PHARMA MATTERS REPORT

Expert therapy area review of the key market players and deals highlights for leading areas of industry investment and development. These insightful reviews are based on the strategic data and insights from Thomson Reuters Cortellis™ for Competitive Intelligence.

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IN THIS ISSUE

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ABSTRACT

Despite the therapeutic advances made over the last decade with the introduction of the immunomodulatory and proteasome inhibitor drug classes, multiple myeloma is still associated with a poor prognosis and has one of the lowest five-year survival rates in oncology. The disease remains incurable, and successfully maintaining remission is an uphill battle. Therapy is complicated by multiple settings and regimens, with a lack of long-term data from large-scale comparative trials to aid treatment choices. Next-generation drugs with improved efficacy and tolerability have now entered the market for heavily pre-treated patients following accelerated approval in the relapsed/refractory setting, but the survival data are currently immature. In the genomics era, steps are being taken towards a more personalized approach to prognosis and treatment; however, this field remains very much in its infancy. It is hoped that further elucidation of the molecular mechanisms of multiple myeloma and pre-competitive research collaborations will enable the rapid development of next-generation targeted therapies in this area of high unmet medical need.

SECTION I

INTRODUCTION

Multiple myeloma is the second most common hematological cancer worldwide, with an estimated 22,000 new cases and over 10,000 deaths expected in the US in 2013 and an approximately equivalent incidence in Europe. As increasing age (> 65 years) is a risk factor for the disease, the incidence of multiple myeloma is expected to rise along with increasing life expectancies.

Multiple myeloma results from the clonal proliferation of plasma cells at multiple sites within the bone marrow, eventually resulting in bone marrow failure and bone destruction. Bone lesions and/or osteoporosis are hallmarks of the disease, observed in 80 percent of newly diagnosed patients, along with elevated calcium levels as a result of bone destruction. Accumulation of malignant cells displaces normal, functional plasma cells from the bone marrow, resulting in anemia, leukopenia and thrombocytopenia. The myeloma cells secrete excessive amounts of all or part of a monoclonal immunoglobulin (M protein) that lacks immunological function. Accumulation of M protein may occur in various organs. Deposition in the kidneys is particularly problematic and causes renal failure in approximately 40 percent of patients.

The development and approval of Velcade has been one of the most rapid in the cancer field

The disease is broadly divided into three main subtypes according to the presence or absence of symptoms and disease progression. Smoldering, asymptomatic multiple myeloma is responsible for approximately 15 to 20 percent of diagnoses and is characterized by serum M protein > 3 g/dl and/or bone marrow plasma cells >/= 10 percent, plus the absence of symptoms such as anemia, renal failure, hypercalcemia and bone lesions. Indolent, asymptomatic disease is also characterized by a lack of overt symptoms and defined as stable serum or urine M protein, with the presence of bone marrow plasmacytosis, and mild anemia or a small number of osteolytic lesions. Finally, symptomatic multiple myeloma is defined as presence of M protein in serum or urine, bone plasmacytosis > 30 percent, and the presence of anemia, renal failure, hypercalcemia and/or osteolytic bone lesions. Patients with active, symptomatic disease are generally stratified into three risk groups using the International Staging System, which assesses risk on the basis of serum beta2-microglobulin and albumin.

Historically, multiple myeloma was associated with a median survival of just seven months. With the advent of chemotherapeutic drugs such as melphalan in the 1960s, and later high-dose chemotherapy and autologous stem cell transplant, newer treatment options resulted in improved median survival times of two to three years. However, while undoubtedly a valuable improvement for patients, the five-year survival rate only increased by nine percentage points over a 30-year period, from 25 percent in 1975 to just 34 percent in 2003. Significant progress in the last decade has again extended survival, with the introduction of immunomodulatory agents Thalomid (thalidomide) and Revlimid (lenalidomide) and the proteasome inhibitor Velcade (bortezomib) resulting in further improvements to median survival times, which now approach seven to eight years. These three agents are excellent examples of translational cancer research following their rapid advancement from bench to the clinic, particularly Velcade, which progressed from first-in-human studies to US approval in just four and a half years. However, despite these valuable advances, multiple myeloma is still associated with one of the lowest five-year cancer survival rates of just 38 percent.

FRONT-LINE THERAPY

THE TRANSPLANT-ELIGIBLE SETTING: TREATMENT DECISIONS AND COMMERCIAL OPPORTUNITIES

For symptomatic multiple myeloma, patients are broadly categorized into transplant-eligible and transplant-ineligible. Transplant-eligible patients are generally those under the age of 65 with no comorbidities. In newly diagnosed eligible patients, high-dose chemotherapy followed by autologous stem cell transplant is the current standard of care. Pharmacotherapy is required at several steps in the procedure, most importantly in the induction and maintenance settings. Historically, an induction regimen of vincristine, doxorubicin and dexamethasone was considered the standard of care, but this combination is rapidly being displaced by more efficacious regimens containing Velcade, Revlimid or Thalomid in combination with dexamethasone, due to better responses observed with these newer agents. Currently Thalomid, Revlimid and Velcade are not approved in the maintenance setting.

Following transplant, oncologists must decide whether to adopt a "watch and wait" approach until disease relapse, or whether the patient should undergo further treatment in an effort to sustain the response achieved with transplant. Currently, most patients will relapse and so maintenance pharmacotherapy has been suggested to prolong disease response and survival. The biggest challenge is how to achieve responses without significantly compromising quality of life.

Traditional maintenance agents include the corticosteroids prednisone and dexamethasone, but their use has been questioned due to the significant morbidity associated with long-term therapy and the lack of overall survival benefit. Thalomid has demonstrated improved progression-free survival in several studies; however, improvements in overall survival have been variable and the drug is associated with significant toxicities such as peripheral neuropathy, constipation and somnolence.

While structurally similar to Thalomid, Revlimid's greater tolerability may be of particular advantage in the maintenance setting. The use of Revlimid as maintenance therapy is supported by the IFM-2005-02 and CALBG100104 studies, which have demonstrated benefits in progression-free survival and time-to-progression, respectively. While not associated with Thalomid's neurological toxicity, Revlimid is associated with significant toxicities such as neutropenia, thromboembolic events and a risk of second primary malignancies, which may limit the duration of therapy.

Velcade may also have potential in post-transplant maintenance therapy, although the drug's intravenous dosing may put the therapy at a disadvantage compared with the orally available Thalomid and Revlimid. Subcutaneous administration has been approved for Velcade's currently authorized uses (which do not include maintenance therapy), and is associated with greater patient convenience and a significantly lower incidence of peripheral neuropathy. While subcutaneous administration is certainly a step forward in terms of convenience, the drug must still be reconstituted and administered by a healthcare provider and is therefore still at a disadvantage compared with oral therapies. Due to the potential for long-term administration in the maintenance setting, convenience is the key to patient compliance.

Maintenance therapy may be a lucrative opportunity in the transplant setting as treatment may be required for several years. However, financial analysts disagree on just how large an opportunity this market segment represents. It is estimated that only 25 percent of eligible patients undergo transplant due to cost and reimbursement issues, or physician preference for other treatment approaches. Novel combinations of newer, more efficacious agents have also contributed to an overall decline in the use of autologous stem cell transplant, and the availability of these therapies has resulted in questioning the role of transplant as the standard of care for eligible patients. Potential caps on extended dosing due to toxicity concerns could also limit opportunities in the post-transplant maintenance setting.

TRANSPLANT-INELIGIBLE PATIENTS: COMPLEXITY OF FIRST-LINE TREATMENT CHOICE

At least 70 percent of newly diagnosed multiple myeloma patients are not eligible for transplant due to advanced age or health complications; consequently, the first-line, transplant-ineligible setting represents the largest market opportunity in multiple myeloma. In addition to the larger potential patient pool, the duration of treatment is markedly longer than in the pre-transplant and relapse settings. However, with the availability of multiple agents in numerous combinations and a lack of phase III data from randomized head-to-head studies, selection of the optimal first-line regimen is challenging.

Selection of a treatment plan typically depends upon local availability and physician preference. Prior to the introduction of newer agents, the combination of melphalan and prednisone was widely regarded as the gold standard. The superior responses observed when Thalomid, Revlimid or Velcade are added have resulted in incorporation of these drugs into front-line regimens. Thalomid and Velcade were first approved for front-line use in 2006 and 2008, respectively; however, the use of Revlimid in the first-line setting is currently not approved in any market.

MARKET DYNAMICS IN THE FIRST-LINE, TRANSPLANT-INELIGIBLE SETTING

Although the incorporation of Thalomid into chemotherapy regimens changed the treatment paradigm for transplant-ineligible patients, studies carried out by the GIMEMA and NMSG groups have shown inconsistencies in the drug's benefit on overall survival, and Thalomid is also associated with significant toxicities such as peripheral neuropathy and venous thromboembolic events. The use of Thalomid is declining in the US following positive data from the VISTA and MM-015 studies supporting first-line use of Velcade and Revlimid, respectively. In fact, Revlimid is already outstripping Thalomid in the first-line transplant-ineligible setting, despite use in this patient group remaining off-label at present. With its tolerability benefits, Revlimid is favored in patients requiring a gentler regimen, such as those with existing neuropathy or advanced age.

Revlimid is expected to further displace Thalomid if data from the intergroup head-to-head ECOG E1A06 study prove positive. Data are eagerly awaited from the trial, which is expected to complete in October 2014. Celgene is also conducting the head-to-head FIRST study to compare Revlimid and Thalomid regimens, which could add further weight to Revlimid's dominance in the first-line setting if successful. Primary outcome data are expected in August 2015.

Thalomid remains more of a competitor in Europe, where patients in some countries may not have access to Revlimid or Velcade outside of clinical trials. The greater price of Revlimid may particularly hinder first-line use in the reimbursement-driven European market, and the lack of significant improvement in overall survival compared with melphalan-prednisone in the MM-015 study may also present a barrier to reimbursement in this region. Celgene had previously filed for European approval of Revlimid in newly diagnosed patients; however, the application was later withdrawn in June 2012 following a request from the Committee for Human Medicinal Products for more mature data to confirm the drug's benefit-risk profile. The company expects to resubmit the filing later this year. Thalomid could also see continued use in patients unable to tolerate Revlimid and Velcade, who account for approximately 10 percent of patients.

Revlimid will need to demonstrate a clear overall survival advantage to penetrate the first-line European market

Velcade-containing regimens are favored in patients with renal impairment, a risk of deep vein thrombosis, rapidly progressive disease or poor cytogenetic risk factors. Although data from randomized head-to-head studies are currently lacking, a meta-analysis of studies has demonstrated faster and superior overall and complete response rates with Velcade-melphalan-prednisone compared with Thalomid-melphalan-prednisone. Front-line use of Velcade is also supported by the finding that patients relapsing following a Velcade-containing regimen can still achieve responses to Thalomid or Revlimid-based regimens in the salvage setting. Historical and future sales trends for Thalomid, Revlimid and Velcade are presented in Figure 1.

SALVAGE THERAPY

INCREASING COMPETITION IN THE SALVAGE SETTING

The relapsed/refractory setting is currently the most dynamic area of multiple myeloma research and development, as shown by the unprecedented accelerated US approval of two new therapies in quick succession: Kyprolis (carfilzomib) in July 2012 and Pomalyst (pomalidomide) in February 2013. In addition to unmet clinical need, the relapsed/refractory setting presents a large market opportunity, as the lack of a curative therapy and the failure of currently available agents to induce long-term responses results in relapse in the vast majority of patients. The duration of remission generally declines with each successive regimen, and survival of patients refractory to Revlimid and Velcade is typically very poor.

"The accelerated approvals of Kyprolis and Pomalyst in the space of seven months is unparalleled in cancer"

Multiple Myeloma Research Foundation

Following relapse, selection of a salvage regimen first depends on the timing of disease relapse. The first-line regimen may be reinitiated if relapse occurs more than six months after completion of the primary treatment course. When relapse occurs within six months, patients typically receive a chemotherapy backbone regimen with a different targeted agent, for example Velcade in patients relapsing after a Thalomid-containing regimen.

Thalomid has somewhat limited use in the second-line setting due to cross-resistance with Revlimid, particularly considering the popularity of Revlimid as a first-line agent. Opportunities therefore exist for Velcade as a second-line agent, where its use is well-established. Combinations of Velcade and Revlimid or Thalomid have also shown efficacy in relapsed patients, and multi-agent combination therapy is generally recommended for patients with aggressive, relapsed disease.

As the newest additions to the difficult to treat relapsed/refractory setting, Pomalyst and Kyprolis have received much attention. Both products have been approved in the third-line setting for patients who have relapsed after prior therapy with Velcade and either Thalomid or Revlimid, and have shown disease progression within 60 days of completion of the last therapy. The accelerated approvals are based on response rates observed in phase II studies, with long-term impact on survival yet to be determined. Table 1 outlines the main considerations for therapy with Kyprolis and Pomalyst.

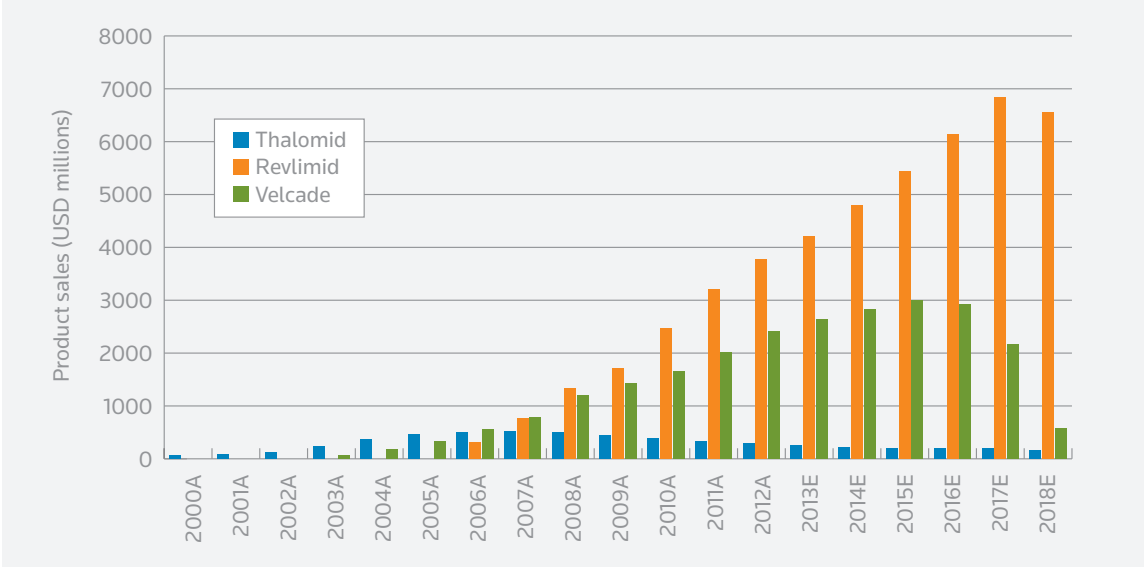

FIGURE 1. THALOMID, REVLIMID AND VELCADE SALES

	KYPROLIS	POMALYST
Dosing	Intravenous over 2 to 10 min on days 1 2, 8, 9, 15, and 16 of a 28-day cycle	Orally once daily on days 1 to 21 of a 28-day cycle
Overall response rate	24[1]	34[2]
Median duration of response (months)	7.8[1]	8.3[2]
Overall survival (%)	15.6[1]	16.5[2]
Main grade 3/4 adverse events	Thrombocytopenia , anemia[1]	neutropenia[2]
Estimated cost per cycle ($)	9,550	10,500

TABLE 1. COMPARISON OF KYPROLIS AND POMALYST

1 003-A1 study (Kyprolis monotherapy)

2 MM-002 study (Pomalyst plus low-dose dexamethasone)

KYPROLIS

Kyprolis is a second-generation irreversible proteasome inhibitor, which provides sustained inhibition compared with first-generation reversible proteasome inhibitor Velcade. Approval is based on the single-arm, phase IIb 003-A1 study of Kyprolis monotherapy in heavily pre-treated, relapsed patients, who had undergone a median of five prior lines of therapy with 80 percent of patients refractory or intolerant to both Velcade and Revlimid. Notable improvements in overall survival were observed, with a median overall survival of 15.6 months comparing very favorably to the nine months typically seen for other therapies in such advanced-stage disease. Similar rates and durations of response were also observed between standard- and high-risk patients and patients dual-refractory to both Velcade and Revlimid, supporting broad use of Kyprolis in the relapsed/refractory setting. Onyx is conducting the phase III FOCUS trial of Kyprolis monotherapy and the ASPIRE trial assessing Kyprolis as an addition to a Revlimid-dexamethasone regimen, both in relapsed/refractory patients, to support registration in Europe, with ASPIRE data also expected to support full US approval. Interim data from FOCUS are expected in the second half of 2013 and will be eagerly anticipated to see if efficacy can match the promising phase II results.

Kyprolis's major advantage over Velcade is its improved tolerability profile; the drug has a markedly lower incidence of peripheral neuropathy, Velcade's most significant toxicity, even compared with subcutaneous Velcade. Kyprolis has also demonstrated a lower incidence of grade 3/4 neutropenia compared with newly-approved competitor Pomalyst (11 versus 43 percent for Kyprolis and Pomalyst, respectively). In the 003-A1 study, the most commonly observed grade 3/4 adverse events were thrombocytopenia (29 percent) and anemia (24 percent). Gastrointestinal symptoms such as nausea were also common, but deemed to be manageable with supportive care. Patients may also require monitoring for dyspnea, which occurred in 34 percent of patients. Data from randomized controlled studies will help to further assess the drug's benefit-risk profile in larger groups of patients.

Kyprolis is being positioned to supersede Velcade in the second- and third-line settings; the multinational head-to-head ENDEAVOUR study is comparing Kyprolis and Velcade, both in combination with low-dose dexamethasone, in patients who have relapsed after no more than three prior regimens. However, with ENDEAVOUR completion not expected before 2018, displacement of Velcade could remain some way off. The ASPIRE study is also aiming to support earlier-line combination use, assessing the benefits of adding Kyprolis to Revlimid-dexamethasone in patients treated with no more than three prior lines of therapy.

Onyx is also conducting studies in newly diagnosed, transplant-ineligible patients to support first-line use of Kyprolis, with the phase III CLARION study expected to begin enrollment imminently. As another head-to-head study, positive data could support expansion of Kyprolis into the front-line setting, potentially providing more ammunition against Velcade if a survival benefit is observed.

With Velcade going off-patent in the US in 2017 and generic Paragraph IV challenges currently in litigation, Onyx must work rapidly to demonstrate the superiority of Kyprolis before generic Velcade reaches the market. However, a potential drawback of Kyprolis is its inconvenient dosing schedule, which requires intravenous infusions on two consecutive days each week, for the first three weeks of a 28-day cycle. With subcutaneous administration now authorized and weekly administration shown to reduce toxicity, Velcade's greater convenience over Kyprolis may present a barrier to loss of market share. Reimbursement issues may also hinder movement of Kyprolis into the front-line, with healthcare payors only authorizing use when other options have been exhausted.

Despite these issues, high demand is expected due to Kyprolis's improved potency and tolerability; Onyx estimates from earlier this year show strong physician adoption, with a 25 percent market

share in the third- and subsequent-line settings after just five months on the market. Consensus forecast data from Thomson Reuters Cortellis for Competitive Intelligence predict rapid achievement of blockbuster status for Kyprolis, with sales exceeding the billion-dollar mark by 2016. Analysts expect Kyprolis to garner peak worldwide sales of up to $2 billion.

POMALYST

Celgene's oral third-generation immunomodulatory drug Pomalyst (an analog of Thalomid) is the newest therapy to enter the market for relapsed/refractory patients, following accelerated FDA approval in February 2013. In the US phase II registration study (MM-002), patients had undergone a median of six prior therapies, including Revlimid and Velcade, with 63 percent of patients refractory to combination Revlimid-Velcade treatment. The study also included patients who were refractory to Kyprolis. The median duration of response was 8.3 months and median overall survival was 16.5 months, comparing favorably to the survival responses seen with Kyprolis and almost double those typically seen for established agents in heavily pre-treated patients. Pomalyst's potency far outstrips that of earlier generation immunomodulatory drugs Thalomid and Revlimid, allowing use at much lower doses (4 mg per day, compared with 25 and 200 mg for Revlimid and Thalomid, respectively). Based on early data, Pomalyst is expected to displace Thalomid in the refractory setting, where approximately 25 to 30 percent of patients are refractory to both Revlimid and Velcade.

While phase III data are yet to be reported for Kyprolis, promising data for Pomalyst from the phase III NIMBUS (MM-003) study were presented at the American Society of Hematology meeting in December 2012. Significant improvements in progression-free and overall survival were observed for Pomalyst plus low-dose dexamethasone compared with high-dose dexamethasone in patients who had received at least two prior lines of therapy. Unlike Kyprolis, Pomalyst is not currently being evaluated in the first-line setting.

While its oral formulation provides significant convenience advantages over Kyprolis, Pomalyst's label is less favorable in terms of safety. Like earlier generation immunomodulatory drugs, Pomalyst carries a boxed warning for embryo-fetal toxicity and venous thromboembolism, and will only be available through a restricted distribution system due to its teratogenic potential. The most notable grade 3/4 adverse event observed in the phase II study was dose-related neutropenia, observed in over half of all patients and requiring supportive treatment in 36 percent of patients at the highest authorized dose (4 mg). Thromboprophylaxis is also likely to be required due to the potential for deep vein thrombosis and pulmonary embolism.

Pomalyst is currently under review in the European Union and may beat Kyprolis to the market in this region, with a decision expected later this year from the European Medicines Agency. Like Kyprolis, Pomalyst is also predicted to achieve sales in excess of $1 billion, although Consensus forecast data from Cortellis for Competitive Intelligence predict that Kyprolis will nudge ahead in terms of 2018 sales ($1660 and $1285 billion for Kyprolis and Pomalyst, respectively). A comparison of sales estimates is given in Figure 2.

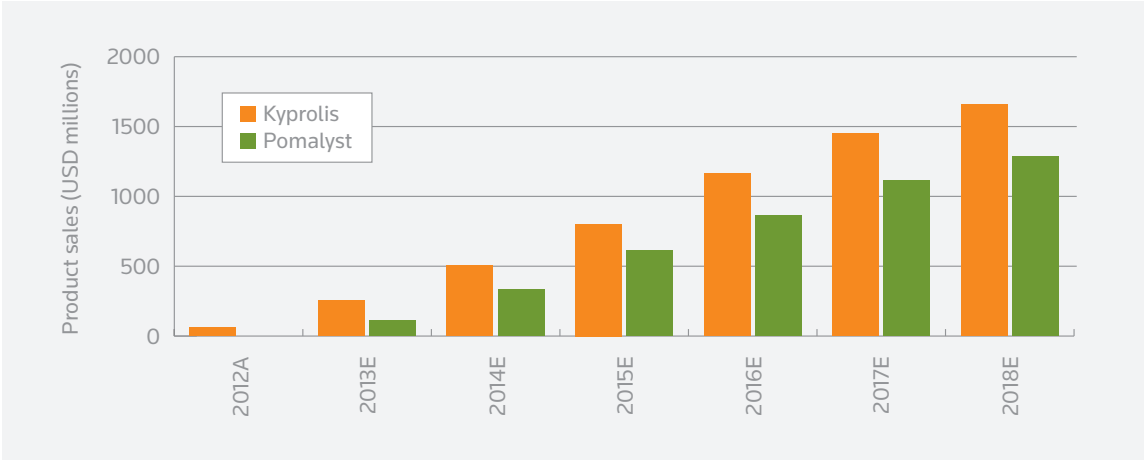

FIGURE 2. CONSENSUS SALES ESTIMATES FOR KYPROLIS AND POMALYST

As survival data for both Kyprolis and Pomalyst are still relatively immature and comparative data with established regimens are lacking, the optimum use of these agents remains to be elucidated. Larger, randomized controlled trials are necessary to further establish which patients will benefit from specific regimens. However, the ability to demonstrate clear improvements in endpoints such as overall survival is becoming more complex for novel drugs, with longer study durations required to tease out any additional benefits over the first- and second-generation immunomodulators and proteasome inhibitors. A number of studies are underway to assess these two new agents in various regimens, including the combination of Pomalyst and Kyprolis in relapsed/refractory patients. As Kyprolis and Pomalyst belong to different classes, combining the drugs could lead to even greater improvements in response, particularly considering the greater efficacy observed when previous generation products Revlimid and Velcade are combined. The greater tolerability of these new agents compared with their forerunners may also be of benefit for combination therapy, which has historically been associated with increased toxicity.

NEXT-GENERATION PROTEASOME INHIBITORS

With the successes of Velcade and now Kyprolis firmly establishing the proteasome as a valuable target for the treatment of multiple myeloma, next-generation proteasome inhibitors have now entered the clinic. Millennium Pharmaceuticals is developing ixazomib citrate as a successor to Velcade, currently the most advanced pipeline product and potentially the first oral proteasome inhibitor to market, with regulatory submissions anticipated in 2015. The compound was selected based on improved bioavailability, tolerability and enhanced tissue penetration over Velcade. Phase III studies are currently underway in the relapsed setting, with trials in newly-diagnosed patients also planned. The phase III TOURMALINE-MM1 study in relapsed/refractory patients is investigating what could potentially be the first all-oral novel drug regimen, consisting of ixazomib citrate, Revlimid and dexamethasone in a convenient dosing schedule of once-weekly ixazomib citrate and dexamethasone with once-daily Revlimid. The combination has shown promising efficacy in phase II studies in treatment-naive patients with an overall response rate of 92 percent. As a monotherapy administered twice-weekly in relapsed/refractory patients, disease control was observed for up to 11.3 months.

Onyx is developing the third-generation proteasome inhibitor oprozomib, an orally bioavailable analog of Kyprolis currently in phase I/II development. Interim data from the phase Ib portion of a study in patients with hematological malignancies (including multiple myeloma) have demonstrated preliminary anti-tumor activity in the small evaluable population. Similarly to Kyprolis, the most common grade 3/4 adverse event was thrombocytopenia. Synergistic activity with Velcade and entinostat (a pan-HDAC inhibitor) and additive activity with Revlimid and dexamethasone has also been observed in preclinical studies, supporting combination use with earlier generation proteasome inhibitors and other drug classes.

The potential for oral dosing could vastly improve patient convenience compared with the injectable first- and second-generation proteasome inhibitors, with their regular intravenous administration described as "life-ruining." Both Millennium and Onyx are hoping to replicate their successes with Velcade and Kyprolis with these more tolerable and convenient therapies.

Other next-generation proteasome inhibitors in the clinic include marizomib and delanzomib; however, their intravenous dosing may put these compounds at a disadvantage compared with their more advanced oral competitors.

APPLICATION OF PERSONALIZED MEDICINE

CYTOGENETICS AND PATIENT STRATIFICATION

It is now well established that multiple myeloma is a distinctly heterogeneous disease, with numerous genetic abnormalities identified. Genomic events may occur simultaneously, and may also be followed by further deletions and secondary translocations. These genetic abnormalities have provided important prognostic information, and although cytogenetic analysis is not yet routinely included in disease staging systems, the Mayo Clinic has recently released updated guidelines

for disease stratification and risk-adjusted therapy (mSMART) recommending cytogenetic evaluation for all patients at diagnosis. The National Comprehensive Cancer Network also recommends a prognostic assessment to identify patients with high-risk cytogenetics.

Genetic events are categorized into two main subtypes: hyperdiploidy and chromosomal structural changes. Hyperdiploidy is generally associated with a better prognosis compared with structural changes. The most commonly seen abnormalities are trisomies of odd-numbered chromosomes such as 3, 5, 7, 9, 11, 15, 19, and 21.

Of the chromosomal changes, deletion of chromosome 17p13 is associated with the poorest prognosis, and deletion of chromosome 13 has also been associated with short event-free and overall survival. Translocations are very common, particularly translocations of the immunoglobulin heavy chain gene (IGH) at 14q32, estimated to be present in approximately 40% of patients. One of the most important translocations is t(4; 14), which results in over-expression of the oncogene MMSET, causing histone modifications that promote cellular functions such as survival, cell cycle progression and DNA repair. This translocation has been identified in 10 to 15 percent of patients and was first associated with a poor prognosis due to shorter periods of remission and more aggressive relapses. However, the finding that patients with t(4; 14) are more responsive to Velcade-containing regimens has led to improved outcomes in this patient subset and reclassification as intermediate risk.

Mayo's 2013 mSMART guidelines suggest stratification of patients into three risk groups based on cytogenetic profiling, as set out in Table 2.

THERAPEUTIC DECISION-MAKING IN THE ERA OF PERSONALIZED MEDICINE

Based on the cytogenetic stratification of newly diagnosed patients, the mSMART guidelines recommend different regimens for standard-, intermediate- and high-risk patients based on potential for disease progression and response to therapy. In high-risk patients, more aggressive and continuous therapy is warranted; a regimen of Velcade-Revlimid-dexamethasone is recommended with indefinite duration. As Velcade has been shown to be particularly beneficial for patients with t(4; 14), first-line use of proteasome inhibitors can be justified in this patient subset; the mSMART guidelines recommend Velcade in combination with melphalan-prednisone or cyclophosphamide-dexamethasone, followed by indefinite Velcade maintenance. Regimens with lower toxicity are recommended for standard-risk patients in order to maximize quality of life, such as Revlimid-low-dose dexamethasone or Thalomid-melphalan-prednisone.

Clear demonstration of benefit with particular drugs or regimens in certain patient subgroups has important implications for patient access, and may allow for reimbursement of therapies normally reserved for later line use. Velcade, and potentially next-generation proteasome inhibitors, could particularly benefit from a more stratified approach to treatment, supported by VISTA study data which showed that patients with high risk cytogenetics had similar response rates, progression-free and overall survival compared with standard risk patients when treated with a Velcade-containing regimen.

The benefit of Revlimid in t(4; 14) patients has also been evaluated, but evidence to support use of this agent is weaker compared with that for Velcade and retrospective studies have drawn different conclusions. Prospective studies are needed to further assess if Revlimid has any additional benefit in this patient subset.

RISK GROUP	KEY CYTOGENETIC MARKERS	MEDIAN OVERALL SURVIVAL (YEARS)	PROPORTION OF PATIENTS (%)
Standard	t(11; 14), t(6; 14)	8 – 10	60
Intermediate	t(4; 14), del13	4 – 5	20
High	del 17p, t(14; 16), t(14; 20)	3	20

TABLE 2. PATIENT STRATIFICATION ACCORDING TO THE 2013 MSMART GUIDELINES (MAYO CLINIC, APRIL 2013)

FIRST STEPS TOWARDS PERSONALIZED THERAPIES

Genome sequencing has identified recurrent mutations in patients with multiple myeloma, potentially enabling development of the first personalized therapies. Results from the first study to simultaneously sequence multiple genomes were published in 2011, providing an unprecedented level of insight into multiple myeloma at the genomic level. The research identified 10 genes with significant mutation rates, including six which had not previously been known to be involved in cancer. Mutations in genes involved in RNA processing and protein homeostasis were found in 42 percent of the 38 patients studied, potentially offering new targets for rational drug design. With a greater understanding of multiple myeloma and interactions in the bone marrow milieu has come an explosion of potential new targets and drug classes, a selection of which are summarized in Table 3.

DRUG CLASS	EXAMPLES
Monoclonal antibodies	elotuzumab, siltuximab, daratumumab, tabalumab
BRAF inhibitors	Vemurafenib
HDAC inhibitors	vorinostat, romidepsin, panobinostat, ricolinostat
Aurora kinase inhibitors	Alisertib
MEK inhibitors	trametinib DMSO
FGFR3 inhibitors	RG-7444
CDK inhibitors	palbociclib, dinaciclib, AT-7519
BCL antagonists	Navitoclax
HSP90 inhibitors	Ganetespib
BTKi inhibitors	ibrutinib, CC-292

TABLE 3. NEW DRUG CLASSES CURRENTLY BEING INVESTIGATED IN MULTIPLE MYELOMA

The presence of BRAF mutations was hailed as a significant find, supporting the investigation of BRAF inhibitors in multiple myeloma, in addition to inhibitors that act downstream of BRAF such as those targeting mitogen-activated/extracellular signal-regulated protein kinase (MEK). With BRAF inhibitors now an established drug class with the market entry of Zelboraf (vemurafenib) for melanoma, it is hoped that BRAF inhibitors will be swiftly investigated for their efficacy in multiple myeloma. Indeed, Roche has already picked up the ball with a phase II trial of Zelboraf underway to assess its efficacy in various BRAF V600 mutation-positive cancers, including multiple myeloma.

MEK inhibitors could be beneficial for patients with high-risk translocations such as t(14; 16) and t(14; 20), which cause over-expression of the oncogene MAF, resulting in increased myeloma cell proliferation and adhesion. Preliminary in vitro studies have shown that MEK inhibitors induced apoptosis and halted proliferation in multiple myeloma cell lines with t(14; 16) and t(4; 14), and resulted in enhanced cytotoxicity when combined with Velcade, Revlimid or dexamethasone. Early-stage clinical studies are currently underway to further assess the potential of MEK inhibitors for the treatment of multiple myeloma. An interesting concept is the combination of targeted therapies; GlaxoSmithKline is conducting a phase I/II study evaluating the oral combination of its MEK inhibitor trametinib DMSO and its AKT inhibitor afuresertib in patients with proteasome inhibitor-refractory multiple myeloma. Study completion is expected in 3Q13, and could provide the rationale for novel targeted treatment combinations.

In addition to the subgroups defined by cytogenetic stratification, further subtypes of multiple myeloma are now being discovered at the molecular level. Gene expression profiling has identified seven distinct subgroups of multiple myeloma; of these subtypes, the MMSET/FGFR3 and MAF groups have been associated with poor rates of overall survival. It is hoped that elucidation of MMSET crystal structure will enable structure-function-based drug design for the development of MMSET inhibitors, a first for rational drug development in this disease.

Another exciting advancement is the development of monoclonal antibodies, in the hope that multiple myeloma will find its equivalent to Rituxan (rituximab), which significantly improved survival outcomes in B cell non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Several monoclonal antibodies with divergent mechanisms of action have reached late-stage clinical development, with elotuzumab (anti-CS-1), siltuximab (anti-IL-6) and tabalumab (anti-BAFF) currently being investigated in phase III trials. Elotuzumab has shown promising activity in combinations with Revlimid and Velcade, potentially supporting a treatment paradigm similar to Rituxan-containing regimens for NHL and CLL, in which the monoclonal antibody is combined with chemotherapy.

These findings offer hope that multiple myeloma may soon benefit from personalized therapies in a similar fashion to BRAF V600E mutation-positive melanoma and ALK-positive non-small-cell lung

cancer, for which Zelboraf and Xalkori (crizotinib), respectively, were rapidly advanced through the clinic and onto the market. However, with just 4 percent of patients identified as carrying BRAF mutations in the 2011 study, the commercial potential of personalized therapies such as BRAF inhibitors for multiple myeloma may be limited by a small eligible patient population. Larger scale genomic sequencing studies are required to more fully assess the frequency of mutations in multiple myeloma. Efforts to achieve this are already underway. In the hope of rapidly advancing development of personalized therapies, the Multiple Myeloma Research Foundation (MMRF) has launched the Personalized Medicine Initiative, a pre-competitive consortium joined by several pharma companies including Bristol-Myers Squibb, Millennium and Onyx Pharmaceuticals.

"Innovation of this magnitude requires a bold, ambitious, and highly collaborative approach to science"

Kathy Giusti. Founder and CEO, MMRF and Multiple Myeloma Research Consortium

The cornerstone of the Personalized Medicine Initiative is the COMMpass study, which aims to analyze genetic information from approximately 1000 multiple myeloma patients in order to guide personalized treatment decisions and inform the design of next-generation targeted therapies.

However, standardized testing for gene expression profiling is not yet available and the use of targeted agents remains to be validated in large-scale trials. The higher cost and greater resources required for parallel therapeutic and diagnostic development may impact advancement of personalized medicines, due to the requirement for in-house diagnostic capabilities or partnerships with specialized companies. One of the biggest barriers to the adoption of personalized therapies in the general clinical setting is the requirement for cheap, simple diagnostic tests that can be uniformly used across practices. Reimbursement of diagnostic tests may also present a hurdle to uptake, particularly for healthcare payors that do not account for the value of the test and base reimbursement decisions on time and cost. Widespread adoption of personalized medicine will require significant education of researchers, industry, regulators and payors.

CONCLUSION I

Thalomid, Revlimid and Velcade have significantly improved outcomes for multiple myeloma patients across treatment settings; however, questions remain over the best use of these therapies and long-term survival outcomes are still relatively poor. Combinations of these agents show promise for improving responses, particularly in patients with aggressive disease, but at the risk of increased toxicity. With the next-generation agents Kyprolis and Pomalyst now on the market for relapsed/refractory patients, there is much interest in how these new products will fit into the treatment paradigm and which regimens will be most efficacious. With a greater understanding of multiple myeloma at both the cytogenetic and molecular levels, a more personalized approach to prognosis and therapy is expected to play a bigger role in disease management if patient access hurdles can be overcome.

SECTION II

DEAL HIGHLIGHTS

Deals coverage from Cortellis for Competitive Intelligence indicates that more than 560 deals related to multiple myeloma have been forged since 1986.

The following section reviews the licensing portfolio of a number of multiple myeloma drugs on the market, as well as certain significant and promising therapeutic multiple myeloma candidates, as featured in Cortellis for Competitive Intelligence. Other notable and high-value deals are also highlighted to give an insight into the multiple myeloma market.

IBRUTINIB: EXTENSIVE PARTNERSHIP ACTIVITY

With expected sales of $2.7 billion in 2017, Celera's ibrutinib has been involved in a high number of agreements compared to other multiple myeloma therapies reported on Cortellis for Competitive Intelligence. Along with Thalomid, this therapy has been the center of six partnerships.

In fact, Pharmacyclics formed a five-year cooperative research and development agreement (CRADA) with the National Cancer Institute's (NCI) Division of Cancer Treatment and Diagnosis (DCTD) in August 2011 to support development of ibrutinib, whereby the DCTD planned to sponsor phase I and II trials in certain hematological malignancies including multiple myeloma and non-Hodgkin lymphoma. Financial details were undisclosed.

Pharmacyclics also acquired certain immune-modulators from Celera Genomics in April 2006, including CRA-024781, a selective HDAC-8 inhibitor, a Factor VIIa inhibitor and B-cell-associated tyrosine kinase inhibitors for lymphoma and autoimmune diseases. Celera would receive $2 million in cash, 0.5 to 1 million Pharmacyclics shares, up to $144 million in milestone payments, plus royalties.

Under the Qualifying Therapeutic Discovery Project (QTDP) program, Pharmacyclics received approval for a November 2010 US grant of approximately $725,000 for the development of PCI-32765, PCI-24781 and PCI-27483.

Pharmacyclics and Janssen Biotech entered into a worldwide collaboration in December 2011 to develop and commercialize Pharmacyclics' PCI-32765 for oncology and other indications, excluding inflammation and immune mediated conditions. Pharmacyclics would receive an upfront payment of $150 million and milestone payments of up to $825 million. Each company would head development on certain indications, while sharing development costs: Pharmacyclics 40 percent and Janssen 60 percent. Pharmacyclics and Janssen would be working to book sales and lead commercialization in the US and outside the US, respectively. Worldwide profits and losses would be equally shared. This initial agreement was followed in August 2012 by two separate milestone payments worth $50 million each for the enrollment of a fifth patient in the SPARK and RESONATE trials. In October 2012, a third milestone payment of $50 million was triggered by enrollment of a fifth patient in the phase III trial (CLL3001).

Janssen and Pharmacyclics' formed a collaboration with Abbott in February 2013 to develop a molecular companion diagnostic test, using Abbott's fluorescence in situ hybridization technology, to identify high-risk chronic lymphocytic leukemia patients who might respond to ibrutinib (financial terms were undisclosed).

LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US $)*
Pharmacyclics	National Cancer Institute	Aug 2011	Unknown
Celera Group	Pharmacyclics	Apr 2006	> 146 million
Pharmacyclics	US Government	Nov 2010	~ 0.72 million
Pharmacyclics	Janssen Biotech	Dec 2011	975 million
Abbott Laboratories	Pharmacyclics	Feb 2013	Unknown
Abbott Laboratories	Janssen Biotech	Feb 2013	Unknown

TABLE 1: SUMMARY OF IBRUTINIB AGREEMENTS

**Approximate values based on the achievement of all milestones for the principal components included in the deal.*

"The agreement with Pharmacyclics is an opportunity to bring a new form of oral therapy to patients with B-cell malignancies"

William N. Hait, MD, PhD. Global Therapeutic Head, Oncology, Janssen

DOMESTIC RIVALRY: CELGENE'S THALOMID, THALOMID ANALOGUES AND MILLENNIUM'S VELCADE

Celgene's Thalomid has been the subject of a variety of patent and development service agreements. With sales revenue of $302 million in 2012, expected to decrease to $159 million in 2018, the partnering activity surrounding this therapy has led to further agreements for its analogues. Celgene assumed responsibility for EntreMed's December 1995 relationship with the NCI for thalidomide by acquiring exclusive worldwide rights to EntreMed's patents and technology for the drug, as well as the FDA orphan drug designations in December 1998.

In August 2001, EntreMed sold its royalty stream from sales of thalidomide to Royalty Pharma. EntreMed received $24.3 million from Royalty and could continue to receive an additional $3 million in sales milestones plus a share of certain royalties.

Celgene and the Rockefeller University's Laboratory of Cellular Physiology and Immunology formed a partnership (by July 1996) in the area of tumor necrosis factor alpha regulation for development of the drug to treat immune system disorders. No financial details were disclosed.

In November 2001, Pharmion was granted exclusive licenses to intellectual property covering thalidomide and the System for Thalidomide Education and Prescribing Safety , as well as preclinical and clinical data. Celgene retained the rights in North America, China, Japan, Korea, and Taiwan and would receive royalties. Celgene also obtained an option to acquire an equity stake in Pharmion and an exclusive option to purchase Penn T, the branch of Penn Pharmaceutical that manufactures Thalomid. If exercised, the option would enable Celgene to receive a 36 percent royalty on all Thalomid sales, including cost of goods sold, and to manage the manufacturing of Thalomid as a wholly owned subsidiary of Celgene. In December 2004, Celgene and Pharmion amended their collaboration, following Celgene's acquisition of Penn T in October 2004; the collaboration was extended from 2005 to 2007. Pharmion was also granted development and marketing rights in Hong Kong, Korea and Taiwan, and Celgene's termination rights, tied to the European Union's approval in November 2006, were removed.

In March 2008, Celgene acquired Pharmion along with all relevant rights to the product. In May 2004, Lipomed was appointed Pharmion's (now Celgene) exclusive distributor of Thalidomide Pharmion 50 mg in Switzerland and Austria and was to stop selling its own formulation of thalidomide in Europe. Both parties agreed to terminate ongoing patent infringement litigation that Pharmion initiated against Lipomed.

Two of EntreMed's Thalomid analogues also became part of Celgene's pipeline, after Pomalyst and Revlimid were licensed for approximately $27 million in January 2003. EntreMed would receive cash payments and equity investments in the form of convertible preferred stock and warrants. Furthermore, Celgene would assume certain EntreMed license payment obligations and would have the option, for one year, to select one of three preclinical products for a research and development collaboration and licensing opportunity with EntreMed. Celgene would also receive an exclusive worldwide license from Children's Hospital to its thalidomide analogue patent portfolio. At the time, experts predicted Pomalyst would generate $1.28 billion in 2018 compared to $6.7 billion in 2017 for Revlimid.

Celgene signed a five-year CRADA agreement with the NCI covering the preclinical and clinical development of Celgene's Immunomodulator-inhibiting drugs (IMiDs), including the two analogues, and SelCIDs programs, including CC-11006 and CC-11050, in June 2000. Financial terms for the CRADA were undisclosed. A trial involving refractory multiple myeloma patients receiving Pomalyst was the center of an August 2008 partnership between the company and Multiple Myeloma Research Consortium (MMRC). The company also invited Innate Pharma

to evaluate the potential clinical synergy of combining Revlimid and Innate's IPH-2101 in a US phase II trial of multiple myeloma patients who had failed first-line therapy in November 2009.

VELCADE

The clinical development of proteasome inhibitor Velcade (another anticancer agent facing competition from Revlimid; expected yield of $579 million in 2018 compared to $2 billion in 2011) was the focus of another CRADA signed under undisclosed financial terms, in January 1999, between ProScript (subsequently LeukoSite, now Millennium) and the NCI.

Ortho Biotech (now Janssen Biotech) and Millennium formed an agreement in June 2003 to develop and commercialize Velcade outside the US for multiple myeloma, while Millennium would retain all US commercialization rights and profits. Millennium retained an option to copromote in certain European countries at a future date. Millennium would receive ex-US royalties, an upfront payment of $15 million and up to $520 million in milestones for multiple myeloma and additional solid and/or hematological cancers. The companies would also jointly form a comprehensive global program to further develop Velcade in the US, the EU and Japan. The partnership was amended to a two-year US copromotion agreement in October 2006, due to start in the first quarter of 2007. Millennium would pay Ortho a commission on excess sales exceeding targets, and a portion of the sales costs. Millennium would maintain responsibility for US commercialization, manufacturing and distribution. The ongoing 2003 ex-US commercialization agreement between the companies continued.

"We believe Ortho Biotech is an outstanding commercialization and development collaborator to fully explore the potential of VELCADE and help deliver this novel oncology product to patients in need around the world"

Barry Greene. President and COO, Alnylam Pharmaceuticals and former General Manager, Oncology, Millennium

In May 2010, Janssen Pharmaceutical (a part of Johnson & Johnson, J&J) and Millennium entered into a Japanese copromotion agreement. In the same year, Pharmstandard and J&J agreed to localize secondary packaging. No financial details were reported for either agreement.

DRUG	LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US $)*
Thalomid	National Cancer Institute	EntreMed	Dec 1995	Undisclosed
	Rockefeller University	Celgene	By July 1996	Undisclosed
	EntreMed	Celgene	Dec 1998	Undisclosed
	EntreMed	Royalty Pharma	Aug 2001	> 27 million
	Celgene	Pharmion	Nov 2001	Undisclosed
	Celgene	Lipomed	May 2004	Undisclosed
Revlimid & Pomalyst	Celgene	National Cancer Institute	Jun 2000	Undisclosed
	EntreMed Inc	Celgene	Jan 2003	>~ 27 million
Pomalyst	Multiple Myeloma Research Consortium	Celgene	Aug 2008	Unknown
Revlimid	Celgene	Innate Pharma	Nov 2009	Undisclosed
Velcade	National Cancer Institute	LeukoSite	Jan 1999	Undisclosed
	Millennium	Janssen Biotech	Jun 2003	>535 million
	Millennium	Janssen Pharmaceutical	May 2010	Undisclosed
	JSC Pharmstandard	Johnson & Johnson	2010	Undisclosed

TABLE 2: SUMMARY OF THALOMID, THALOMID ANALOGUES AND VELCADE AGREEMENTS

**Approximate values based on the achievement of all milestones for the principal components included in the deal.*

SELECTED HIGH VALUE DEALS FOR STRATEGIC DRUGS OF FOCUS

There were a number of high value deals for strategic drugs reported in the strategic drug section of this article. One of them was Janssen Biotech's phase II anti-CD38 human mAb, daratumumab, under license from Genmab. Janssen acquired exclusive worldwide rights in August 2012 for the drug as well as a back-up CD38 human antibody, agreeing to pay Genmab an upfront license fee of $55 million and up to $1 billion in milestones plus tiered double digit royalties. Johnson & Johnson Development, an affiliate of Janssen, would make an equity investment of approximately $80 million (DKK 475 million) to subscribe for 5.4 million new shares at a price of DKK 88 per share in Genmab.

With $556 million projected sales revenue for 2017, PDL BioPharma had divested several of its drugs under development to its spin-off company, Facet Biotech (now a subsidiary of Abbott Laboratories), by December 2008 under undisclosed financial terms. These include CS-1/CD37-targeting human mAb, elotuzumab, along with daclizumab (iv and sc), volociximab, enavatuzumab and PDL-241.

PDL previously signed a worldwide agreement with Bristol-Myers Squibb (BMS) in August 2008, whereby PDL would receive $30 million upfront, milestones of up to $680 million and ex-US royalties, while US profits would be shared. BMS had an option to expand the collaboration to include PDL's immune therapy, PDL-241 by paying PDL an additional cash option payment of $15 million and potential milestones totalling up to $430.

In January 2010, Facet received a $15 million milestone payment from BMS, following patient enrollment for the phase II arm of an ongoing phase I/II study of elotuzumab.

In September 2010, Ono Pharmaceutical acquired Onyx Pharmaceuticals' oprozomib and Kyprolis (expected to yield $1.6 billion in 2018) as part of a deal worth more than $330 million. Included in this deal were the exclusive Japanese development and commercialization rights for use of these drugs in oncology. Onyx would receive an upfront payment of JPY 5 billion (approximately $54 million), milestones of up to approximately $280 million, plus double-digit percentage royalty payments.

"Ono is an ideal partner in Japan given their focus on highly innovative new pharmaceutical products and their reputation for scientific excellence,"

N. Anthony Coles, MD. President and CEO, Onyx

DRUG	LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US $)*
daratumumab	Genmab	Janssen Biotech	Aug 2012	>~ 1.135 billion
elotuzumab	Facet Biotech	Bristol-Myers Squibb	Aug 2008	> 710 million
Kyprolis & oprozomib	Onyx Pharmaceuticals	Ono Pharmaceutical	Sep 2010	>~ 334 million

TABLE 3: SUMMARY OF SELECTED HIGH VALUE DEALS FOR STRATEGIC DRUGS OF FOCUS

*DRU*Approximate values based on the achievement of all milestones for the principal components included in the deal.*

OTHER HIGH VALUE DEALS FOR MULTIPLE MYELOMA

One of the highest value deals related to multiple myeloma reported in Cortellis for Competitive Intelligence was Novartis's November 2009 $1.3 billion acquisition of ex-US development and commercialization rights to myelofibrosis treatment, oral INCB-18424. Also included in that deal were worldwide rights to Incyte's multiple myeloma therapy, INCB-28060, for hematology-oncology indications. Incyte would receive $150 million up front, an immediate $60 million milestone payment for initiation of the phase III COMFORT-II INCB-18424 trial, up to approximately $1.1 billion in further milestone payments, and tiered double-digit royalties. Collaborative study costs would be split. Novartis would be responsible for developing INCB-28060 after phase I; Incyte held on to an option to codevelop and copromote the drug. Incyte continued to receive a further $105 million in milestones.

"...the appreciation from Novartis for INCB18424's potential to treat the unmet patient need in myelofibrosis and other cancers, and their proven success in rapidly commercializing new targeted oncology treatments, were determining factors in our decision to choose Novartis as our collaborative partner."

Paul A. Friedman. President and CEO, Incyte

Novartis continued to show involvement in yet another high value deal for multiple myeloma by forming a three-year alliance with MorphoSys in May 2004. The companies were to use MorphoSys's HuCAL GOLD platform to discover and develop antibodies, including NOV-3, against Novartis-identified targets; a right was reserved to extend the deal term to five years. Novartis would make an approximate EUR 9 million (approximately $11.2 million) investment in MorphoSys by purchasing non-interest bearing convertible bonds in its partner, which could be converted into 490,133 common MorphoSys shares, to be issued from conditional capital. MorphoSys would also receive over $30 million in R&D funding and technology license fees over the first three years, as well as technology license and milestone payments plus royalties. Novartis received a non-exclusive option to internalize the platform, which would trigger a further payment to MorphoSys.

The alliance was expanded in December 2007 by forming a 10-year collaboration worth more than $1 billion, whereby Novartis would use the platform to discover and develop antibodies for a wide range of diseases. MorphoSys would receive annual fees worth more than $600 million, additional milestone payments, R&D funding and profit sharing and/or royalties, while retaining codevelopment rights to selected programs and commercialization rights to specific territories. Novartis gained the option to extend the collaboration for a further two years or to conclude after seven years.

MorphoSys exercised its option in September 2008 to participate in the development of an antibody program in collaboration with, and funded by, Novartis. By March 2009, BHQ-880 had been discovered, which MorphoSys was presumed to have out licensed to Novartis.

Novartis then committed to the 10-year term in July 2009 based on MorphoSys's successful achievement of certain predefined improvements in its technologies. The term would run until 2017 and might be extended by Novartis for two more years; the option to terminate the alliance after seven years was removed. LJM-716 for ophthalmic diseases, BYM-338 for musculoskeletal diseases, VAY-736, and LJM-716 were subsequently disclosed to be part of the agreement.

"We have chosen MorphoSys as the ideal partner for this element of our strategy because of their highly differentiated technology, which we believe will significantly strengthen and accelerate our antibody research"

Dr Mark Fishman. President, Novartis Institutes for Biomedical Research

DRUG	LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US $)*
INCB-18424	Incyte	Novartis	Nov 2009	> 1.310 billion
BHQ-880; BYM-338; HuCAL-based mAb (undisclosed indication), Novartis; LFG-316; LJM-716	Incyte	Novartis	May 2004	> 1.011 billion
dacetuzumab	Seattle Genetics	Genentech	Dec 2000	> 860 million

TABLE 4: SUMMARY OF HIGH VALUE AGREEMENTS FOR MULTIPLE MYELOMA

**Approximate values based on the achievement of all milestones for the principal components included in the deal.*

The potential of dacetuzumab for multiple myeloma therapy was identified by Genentech when it agreed to codevelop Seattle Genetics' CD40 antigen antagonists by December 2000. Although Genentech terminated its development of one the leads, SGN-14, in October 2002, it licensed exclusive worldwide rights to another lead, SGN-40, in January 2007. Seattle would receive $60 million up front, milestone payments exceeding $800 million and escalating double-digit royalties. Seattle received $20 million over the course of the agreement until February 2010, when both companies parted ways. Seattle subsequently discontinued development of the drug in August 2011, along with its anti-psoriatic CD70 antigen inhibitor, vorsetuzumab, to focus its resources on its antibody-drug conjugates.

"Genentech's oncology development expertise, commercial leadership and history of successful strategic alliances make it an ideal collaborator to bring the potential benefits of SGN-40 to patients."

Clay B. Siegall, PhD. President and CEO, Seattle Genetics

CONCLUSION II

Velcade and Thalomid both face competition from Celgene's thalidomide analogue Revlimid. Thalidomid and Revlimid, along with another thalidomide analogue Pomalyst were the subject of a collaboration between Celgene and EntreMed. Celgene initially took over EntreMed's thalidomide relationship with the NCI as part of its own thalidomide development of Thalomid but EntreMed's reason for doing so remains unclear. At the time of the agreement, EntreMed stated it was to use any royalties received from Celgene for the development of Thalomid to support development of the antiangiogenic anticancer agent, Endostatin in its then upcoming clinical trials in 1999. This Thalomid had had no development reported since November 2009.

Celgene followed this up by licensing EntreMed's Revlimid and Pomalyst for $27 million, which are expected to yield a combined total of almost $8 billion in a few years time. Again, the decision remains vague but it shortly followed the mutual dismissal of lawsuits filed against each other regarding patents and applications for Pomalyst, while the funds would allow EntreMed to alleviate its near and medium-term cash needs at the time.

The high interest in therapies targeting this bone marrow cancer is evident with investments from Janssen Biotech and BMS of over half a billion dollars in phase II candidate, daratumumab, which was only in early stage development at the time of the agreement–and phase III candidate, elotuzumab (forecast sales of over $0.5 billion in a few years), which was in phase II trials.

There was also heavy investment from Novartis of more than $2.3 billion in Incyte's early-stage drugs, BHQ-880 and INCB-18424, although no further development for multiple myeloma had been reported for the latter.

With the need to develop further treatments for multiple myeloma and the condensed oncology market for more prevalent cancers, further investment and partnering activity is required to put this hematological disease in a stronger market position.

NOTES

NOTES

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