Conference Insight
The American Society of Hematology Annual Meeting 2013
Datamonitor Healthcare’s analysis of the key highlights

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Overview

Datamonitor Healthcare attended the 55th annual meeting of the American Society of Hematology (ASH), which took place between 7 December and 10 December 2013, in New Orleans, Louisiana. Datamonitor Healthcare has identified the following key highlights from the meeting:

- The results of the second stage of the Phase III CLL11 trial have shown that previously untreated CD20+ chronic lymphocytic leukemia (CLL) patients treated with Gazyva (obinutuzumab; Roche/Biogen Idec) and chlorambucil had a significantly better median progression-free survival compared to patients treated with Rituxan (rituximab; Biogen Idec/Roche/Chugai/Zenyaku Kogyo) plus chlorambucil. These results will enhance Gazyva’s prospects as a potential successor to Rituxan and represent a major milestone for the field of glycoengineering.

- The initial results from the Phase III FIRST trial show that the combination of Revlimid (lenalidomide; Celgene) plus low-dose dexamethasone is superior to the combination of melphalan, prednisone, and Thalomid (thalidomide; Celgene) for the treatment of newly diagnosed multiple myeloma patients that are ineligible for stem cell transplant. These positive results will support Revlimid’s label expansion to the first-line setting of multiple myeloma and establish the drug as the standard of care in this lucrative patient population.

- Results from the Phase III 0116 trial demonstrate that the combination of idelalisib (GS-1101; Gilead) and Rituxan is superior to Rituxan monotherapy for treatment of relapsed or refractory CLL. Idelalisib has the potential to change the CLL treatment landscape by providing an effective therapy option for patients who previously had poor outcomes. Idelalisib will launch in CLL in 2014, but will face intense competition from Imbruvica (imatinib; Pharmacyclics/Johnson & Johnson). The results of ongoing Phase III trials will determine how physicians sequence these exciting new therapies.

**CLL11 trial demonstrates superiority of Rituxan’s glycoengineered successor**

Results from the second stage of the CLL11 trial show that patients treated with Gazyva lived significantly longer without their disease worsening compared to patients treated with Rituxan.

The results of the second stage of the CLL11 trial will help drive uptake of Gazyva as a treatment for CLL. As a potential successor to Rituxan it was imperative for Gazyva to demonstrate superiority in the head-to-head comparison part of the CLL11 trial. The positive results in Gazyva’s favor represent a significant step forward in Roche’s plans to offset revenue loss when Rituxan’s patent expires. Gazyva is the first glycoengineered monoclonal antibody approved for the treatment of cancer and its successful development represents a significant milestone for the field of glycoengineering.
Results from the second stage of the CLL11 trial were presented on Sunday 8 December at the 55th ASH meeting. Dr Valentin Goede of University Hospital Cologne and the German CLL Study Group (GCLLSG) presented the results of the head-to-head comparison of Gazyva plus chlorambucil versus Rituxan plus chlorambucil in treatment-naive patients with CD20+ CLL. Patients in the Gazyva plus chlorambucil arm had a significantly better median progression-free survival (26.7 months) compared to patients treated with Rituxan plus chlorambucil (15.2 months). The complete response (CR) rate was higher in patients treated with Gazyva plus chlorambucil (21%) than in patients treated with Rituxan plus chlorambucil (7%). Infusion-related reactions and neutropenia were more common with Gazyva plus chlorambucil, but there was no increase in infections. Dr Goede concluded that Gazyva plus chlorambucil is superior to Rituxan plus chlorambucil and a highly active treatment in this typical CLL patient population.

Discussing the results of the CLL11 trial at a press conference on the changing treatment landscape for CLL, Dr Goede attempted to put the results in context. He made it clear that the results from the CLL11 trial are impressive but that it is too early to say that Gazyva should replace Rituxan in all treatment settings. When asked if he would say that Gazyva is poised to replace Rituxan, Dr Goede said: “What we currently know is that if we combine [Gazyva] or [Rituxan] with a weaker chemotherapy backbone, [Gazyva] is superior to [Rituxan]. So in this setting I would say that it will substitute [Rituxan]. It is more difficult to say for younger patients where [Rituxan] is combined with more aggressive chemotherapy backbones. These treatments are very effective in these patients and we don’t know how much [Gazyva] adds to the efficacy when replacing [Rituxan].”

The CLL11 Phase III trial enrolled 781 previously untreated CD20+ patients with CLL and co-existing medical conditions. Stage 1 (n=589) compared Gazyva plus chlorambucil to chlorambucil alone and Rituxan plus chlorambucil to chlorambucil alone. Stage 2 (n=663) compared Gazyva plus chlorambucil directly with Rituxan plus chlorambucil. The first part of the CLL11 trial showed that Gazyva plus chlorambucil improved median progression-free survival (mPFS) compared to chlorambucil alone (23.0 months mPFS compared to 11.1 months mPFS). Results from the first part of the CLL11 trial led to Gazyva’s approval for use in combination with chlorambucil to treat patients with previously untreated CLL in the US in November 2013.

Gazyva is the first glycoengineered monoclonal antibody approved for the treatment of CLL, and the first drug with breakthrough therapy designation to receive US Food and Drug Administration (FDA) approval. Gazyva is a third-generation type II humanized anti-CD20 monoclonal antibody (MAb) that selectively binds to the extracellular domain of the human CD20 antigen on malignant human B cells. The Fc region carbohydrates of the antibody have been glycoengineered to improve binding with the FcgammaRIII receptors. This results in enhanced antibody-dependent cellular cytotoxicity (ADCC) and caspase-independent apoptosis.

The results of the second stage of the CLL11 trial clearly enhance Gazyva’s prospects as a potential successor to Rituxan. Rituxan is facing patent expiry within the year in the EU and although US patent expiry is not anticipated until 2018, Roche still needs to prepare for competition with rituximab biosimilars. By demonstrating that Gazyva has superior efficacy to Rituxan in treatment-naive patients with CD20+ CLL, Roche has taken a crucial step toward protecting the revenue generated by Rituxan in that indication. An estimate of how Rituxan’s sales are split by the various indications for which it is approved is shown in the table below.
### Rituxan sales split by indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Percentage of sales</th>
<th>Sales value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sales in 2013*</td>
<td>100%</td>
<td>$7,510m</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>42%</td>
<td>$3,154m</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>25%</td>
<td>$1,877m</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>16%</td>
<td>$1,202m</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>17%</td>
<td>$1,277m</td>
</tr>
</tbody>
</table>

*Note: Rituxan’s total sales estimate for 2013 is approximately double the sales reported in H1 2013

Source = Datamonitor Healthcare

Roche is aiming to demonstrate Gazyva’s superiority to Rituxan in each of the oncology indications for which Rituxan is approved. Gazyva is currently being compared to Rituxan in a Phase III trial for patients with CD20+ diffuse large B-cell lymphoma (GOYA) (ClinicalTrials.gov identifier: NCT01287741). There are also two Phase III trials investigating Gazyva for patients with indolent non-Hodgkin’s lymphoma (follicular lymphoma is an indolent non-Hodgkin’s lymphoma). The first trial is comparing Gazyva and Rituxan as maintenance therapies (GALLIUM) (ClinicalTrials.gov identifier: NCT01332968) and the second trial is investigating Gazyva as a treatment for patients with Rituxan-refractory disease (GADOLIN) (ClinicalTrials.gov identifier: NCT01059630). However, Roche does not appear to be developing Gazyva as a treatment for rheumatoid arthritis.

Gazyva’s approval means that CLL patients will have a new effective treatment option but it also signifies a major milestone for the field of glycoengineering. Glycoengineering has previously been used to create novel therapeutics and vaccines but this is the first time a MAb for the treatment of cancer has been improved by glycoengineering. By altering the Fc region carbohydrates it was possible to enhance ADCC and ultimately to improve treatment outcomes for patients. The successful development of Gazyva has implications for all diseases where MAbs are used as part of treatment because it has demonstrated that glycoengineering antibodies can lead to more effective treatments. Glycoengineered antibodies have been or are currently being investigated in clinical trials for a variety of diseases including cancer, inflammation, and asthma.

**Revlimid shows a significant clinical benefit in newly diagnosed multiple myeloma patients**

**Phase III results will establish Revlimid as the standard of care for the first-line treatment of multiple myeloma**

Initial results from the Phase III FIRST trial show that the combination of Revlimid plus low-dose dexamethasone is superior to the combination of melphalan, prednisone, and Thalomid for the treatment of newly diagnosed multiple myeloma patients.
that are ineligible for stem cell transplant. These positive results will support Revlimid’s label expansion to the first-line setting of multiple myeloma and establish the drug as the standard of care in this lucrative patient population.

Dr Thierry Facon presented the initial results of the Phase III FIRST trial in the plenary session of ASH on Sunday 8 December. The FIRST trial enrolled 1,623 patients from 18 different countries in what was the largest study ever conducted for registration in newly diagnosed multiple myeloma patients. Patients were randomized to receive either a continuous dose of Revlimid and low-dose dexamethasone until disease progression (Rd, n=535), 18 cycles of Revlimid plus low-dose dexamethasone (Rd18, n=541), or 12 cycles of melphalan, prednisone, and Thalomid (MPT, n=547). The median age of patients on the trial was 73 years, and 35% of patients were aged 75 years and over. It was noted that the patient population enrolled on the FIRST trial was highly representative of the general characteristics of patients receiving first-line systemic therapy for multiple myeloma.

The FIRST trial showed that patients receiving Rd demonstrated a superior progression-free survival (PFS) benefit of 25.5 months compared to 21.2 months in patients receiving MPT. Interim analysis of the overall survival data also favored continuous Revlimid dosing, with 59.4% of patients in the Rd arm showing a four-year overall survival benefit, compared with 51.4% of patients receiving MPT. Secondary endpoints such as time to progression also favored patients in the Rd arm of the trial over those receiving MPT (32.5 months vs 23.9 months, respectively).

The treatment-related adverse events associated with continuous Revlimid dosing were found to be manageable in this patient population. The most common grade 3–4 hematological adverse events observed in patients receiving Rd were neutropenia (27.8%), anemia (18.2%), and thrombocytopenia (8.3%), with common grade 3–4 non-hematological adverse events including infections (28.9%) and pneumonia (8.1%). Fewer patients receiving continuous Revlimid discontinued treatment due to adverse events compared to patients receiving MPT (11% vs 14%), and 39% of patients in the Rd arm were still receiving the drug after two years.

A particular focus of the presentation was the occurrence of hematological secondary primary malignancies (SPMs) in patients receiving Revlimid therapy. The overall incidence of these adverse events was found to be lower in patients in the Rd arm of the trial than in patients receiving MPT (0.4% vs 2.2%). As previous trials investigating Revlimid in the first-line treatment setting had indicated that use of the drug led to an increased risk of hematological SPMs when compared to placebo, these results are likely to ease concerns about using Revlimid in newly diagnosed multiple myeloma patients.

The results of the FIRST trial will support Revlimid’s label expansion to the first-line treatment setting of multiple myeloma and establish the drug as the standard of care in this patient population. Celgene is planning to submit regulatory applications for Revlimid’s use in newly diagnosed patients in the first quarter of 2014, with the subsequent approvals expected by the end of the year. At this time, continuous dosing of Revlimid and low-dose dexamethasone is likely to become the preferred regimen for the treatment of newly diagnosed multiple myeloma patients that are ineligible for stem cell transplant. Dr Facon also believes that the results of the FIRST trial will lead to Revlimid’s dominance in this treatment setting, stating that: “In newly diagnosed multiple myeloma patients that are transplant-ineligible, the FIRST trial establishes continuous Rd as a new standard of care.”

This prediction could represent a significant commercial opportunity for Celgene. Datamonitor Healthcare estimates that over 16,000 people will be diagnosed with Stage II/III multiple myeloma in the US in 2014, with 53% of these patients ineligible for stem cell transplant. The efficacy and tolerability demonstrated by Revlimid will promote extensive uptake of the drug in this patient population and dramatically increase Celgene’s market share in this lucrative treatment setting.
continuous dosing regimen of Revlimid will also increase the drug’s commercial potential in this treatment setting when compared to other therapies that cannot be tolerated for a similar duration of time.

### Idelalisib proves an effective therapy for relapsed or refractory chronic lymphocytic leukemia

#### Phase III data demonstrate idelalisib can help change the CLL treatment landscape

Results from the Phase III 0116 trial showed that the combination of idelalisib and Rituxan is a more effective therapy for relapsed or refractory CLL than Rituxan monotherapy. These positive results will support marketing approvals in the US and EU, which will address the high unmet need for effective and well-tolerated therapy options for relapsed/refractory CLL patients. Idelalisib will face tough competition from Imbruvica, which is also armed with impressive data and will be approved first in the US market.

On Tuesday 10 December, Dr Richard Furman presented interim data from a Phase III trial of idelalisib in relapsed or refractory CLL. Patients treated with idelalisib plus Rituxan had a significantly improved PFS rate of 93% (after 24 weeks of therapy) compared with patients treated with placebo plus Rituxan (46% at 24 weeks). PFS strongly favored the idelalisib/Rituxan arm in all patient sub-groups. Treatment with the idelalisib/Rituxan combination was also associated with a superior lymph node response rate (93% versus 4%) and overall response rate (ORR) (81% versus 13%) compared with placebo/Rituxan. Median PFS has not yet been reached in the idelalisib/Rituxan group, and was 5.5 months in the placebo/Rituxan group. Overall survival favored the idelalisib/Rituxan arm, but median OS has not yet been reached in either group. The rates of adverse events were similar in both arms, but Dr Furman drew attention to the lower rate of infusion-related reactions in the idelalisib/Rituxan arm (16%) compared with the placebo/Rituxan arm (28%). Dr Furman speculated that this may be “a result of the idelalisib, in a way, impacting on the tolerability of the rituximab infusion.” Dr Furman also made specific reference to a higher rate of transaminitis (elevated transaminase levels, a marker of liver toxicity) in the idelalisib/Rituxan group (35%) compared with the placebo/Rituxan group (19%). Four out of six patients in the idelalisib/Rituxan group who experienced grade 3/4 transaminitis and had their treatment discontinued were successfully rechallenged with idelalisib, and continued to receive therapy.

The Phase III trial enrolled 220 patients with relapsed or refractory CLL. Patients had previously received a median of three prior therapies, and at time of enrollment required treatment for progressive disease but were unfit to receive further cytotoxic chemotherapy. Patients were randomized to receive eight infusions of Rituxan (375mg/sq m cycle 1, 500mg/sq m cycles 2–6) over 24 weeks plus either idelalisib (150mg) or placebo taken orally twice daily. Patients in the idelalisib arm will continue receiving idelalisib, and patients in the control arm (Rituxan plus placebo) are eligible to receive open-label idelalisib therapy in an extension study.

CLL is a malignancy of B-cell lymphocytes, which are memory cells of the body’s immune system involved in producing antibodies to fight infection. CLL is the most common leukemia in the Western world, and Datamonitor Healthcare forecasts that incident cases of CLL in the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) will increase gradually from 32,500 in 2014 to 33,800 in 2023.

Idelalisib is an orally available, first-in-class, small molecule inhibitor of the phosphoinositide-3 kinase (PI3K)-delta isoform. PI3K is a key component of the B-cell receptor pathway, which plays a crucial role in the development, proliferation, and survival of both normal and malignant B-cells.
The positive Phase III data demonstrate that idelalisib can address a key unmet need in CLL treatment: the requirement for effective therapies for patients who are not fit enough to receive cytotoxic chemotherapy. A key use of idelalisib could be as a first-line treatment for patients who cannot tolerate cytotoxic chemotherapy regimens (generally administered in combination with Rituxan). In the Phase III study, all patients were defined as unable to tolerate cytotoxic chemotherapy because of co-morbidities, renal dysfunction, or cytopenias due to poor bone marrow reserve.

Off-label use of idelalisib in the first-line setting may be facilitated by the fact that the Phase III data show idelalisib has strong efficacy as a combination therapy with Rituxan, the current first-line standard of care. Gilead will hope that these positive data will allow idelalisib to benefit from Rituxan’s success in the first-line setting. To boost chances of first-line uptake in the future, it will be important for Gilead to demonstrate that idelalisib can also combine effectively with Roche’s glycoengineered anti-CD20 MAb Gazyva, which looks set to become an important first-line treatment option.

In the coming years, idelalisib will feature among a wave of new drugs that will dramatically change the CLL treatment landscape. In addition to idelalisib, the CLL pipeline currently features exciting candidates like Imbruvica, IPI-145 (Infinity Pharmaceuticals), and ABT-199 (AbbVie). It is currently difficult to assess which of these drugs could become the most commercially successful, or how they might be sequenced in CLL therapy. This will become more apparent in the near future, as data from larger active-controlled trials mature, giving physicians a better idea of how effective these drugs are, and where it is best to use them. The Bruton’s kinase inhibitor Imbruvica is the most advanced candidate, with marketing applications already filed for CLL in the US (in Q2 2013) and the EU (in Q4 2013). Recently announced Phase IIb/II results showed that Imbruvica monotherapy was associated with a 71% ORR in relapsed/refractory CLL patients, with a PFS rate (26 months) of 75%, and an OS rate (26 months) of 83%. Furthermore, data from a Phase II trial presented at ASH 2013 demonstrated the potential efficacy of an Imbruvica/Rituxan combination in high-risk CLL patients. Imbruvica/Rituxan induced partial remission in 87% of patients and complete remission in 8% of patients. IPI-145 is an orally available small molecule inhibitor of PI3K-delta and -gamma isofoms. Phase I data presented at ASH 2013 demonstrated preliminary efficacy of IPI-145 in relapsed refractory CLL (ORR of 48%, nodal response rate of 48%), and Infinity Pharmaceuticals is now enrolling patients into a Phase III registration trial. ABT-199 is an orally available small molecule inhibitor of Bcl-2, a protein involved in the regulation of cell death (apoptosis). Phase I data presented at ASH 2013 revealed that ABT-199 monotherapy was highly active in relapsed/refractory CLL patients, with an ORR of 84% and 21% of patients achieving complete remission of their disease. AbbVie is now investigating ABT-199 in a Phase II trial in CLL patients with chromosome 17p deletions, and is also conducting trials assessing ABT-199 in combination with either Rituxan or Gazyva.

The new efficacy data for idelalisib point to a bright future for the drug in CLL, but initial competition with Imbruvica will limit uptake. Imbruvica will almost certainly be approved in the lucrative US market before idelalisib. Datamonitor Healthcare expects that uptake of both Imbruvica and idelalisib will be rapid due to the clear clinical benefit both drugs provide to patients compared to current relapsed/refractory CLL therapies. Both drugs have impressed so much in clinical development that the FDA has awarded them breakthrough therapy designations in CLL, which will guarantee accelerated approval processes in the US. Datamonitor Healthcare expects that Imbruvica will be approved in the US in Q1 2014, and in the EU in Q3 2014, and that approvals of idelalisib will follow in the US and EU in Q3 2014. A clearer picture of whether either of these therapies will emerge as a standard of care for relapsed or refractory patients may resolve when data from ongoing Phase III clinical trials of these drugs in CLL emerge.