ONXEO
THE ORPHAN ONCOLOGY INNOVATOR

SHAREHOLDER LETTER – SEPTEMBER 2015

Dear Sir or Madam, Dear Shareholders,

As announced, this new issue of our shareholder letter is devoted to Beleodaq®, a topic specifically discussed at the recent analyst presentation held in Paris. Indeed, besides commenting on our half-year results, Graham DIXON, CSO and Head of R&D, reviewed our orphan oncology portfolio, and, more in-depth, Beleodaq®, currently developed for the treatment of peripheral T-cell lymphoma (PTCL), a rare blood cancer.

In this letter, you will find details on PTCL, the characteristics of belinostat (the active principle at the core of Beleodaq®), the detailed mode of action of the treatment, and interviews with Prof. Jean-Louis Misset, MD and Karsten Witt, MD who give us their view on the disease, the profile of Beleodaq®, as well as its potential.

You will also find a series of questions that were asked by the attendees at our analyst meeting and the answers that were given.

Beleodaq® is key to our strategy, and this letter is aiming at sharing a better understanding about this important drug of our orphan oncology portfolio.

Sincerely yours

Judith GRECIET, CEO

CONTENTS

PTCL: A SEVERE DISEASE EXPLAINED BY A CLINICIAN

Emeritus Professor at the Faculty of Medicine Paris 7, Professor Jean-Louis MISSET has treated patients throughout his career at the Saint Louis Hospital in Paris and at the Paul Brousse Hospital in Villejuif. He is the former president of the scientific advisory board of Topotarget and has published more than 200 scientific articles.

PTCL in figures

The incidence is estimated to 15,500 new patients each year in the US, Japan, and top-5 EU countries. The prevalence is higher in the US and in Asia. Patients are most often diagnosed in their 60s. There tends to be more males (55%) than females.

Can you describe Peripheral T-cell Lymphoma (PTCL)?

PTCL (or Peripheral T-Cell Lymphoma) is a subtype of non-Hodgkin's lymphoma (NHL). NHL are tumors, mainly located in the lymph nodes. NHL affects lymphocytes, white blood cells that help fight infection and are located in the lymphatic system. When affected, their growth or behavior is uncontrolled. They can form tumors called lymphoma.

NHL can be split in numerous and polymorph sub-groups of cancers, of which Peripheral T-Cell Lymphoma is one. In 15% of cases, NHL arises in immune cells called T-cells. These immune cells are incepted in the bone marrow, migrate to the thymus to continue their maturation and finally go into the blood and lymph where they are involved in immune defense. PTCL is called “peripheral” as it affects mature T-cells especially in the lymph nodes. However, it may sometimes affect organs or other tissues such as bone marrow, liver, lungs, etc. This cancer generally progresses rapidly and tends to spread, hence its aggressive nature.

How is PTCL diagnosed? What is the prognosis?

The symptoms vary greatly, but generally fever or fatigue are associated with palpable tumor ganglion masses. These cancers, though rare, are well-known and rapidly diagnosed thanks to the biopsy of a lymph node in general. It is extremely severe and at this point, the treatment options remain limited.

In average, survival time in PTCL is of the order of 3 to 4 years. The tumors tend to spread to other organs and/or not to respond to treatment. They can also relapse. Therefore, patients will have to undergo several rounds (called lines) of treatments, often associated with side effects.

PTCL: A DISEASE FOR WHICH NEW OPTIONS ARE NEEDED

Strong unmet medical need

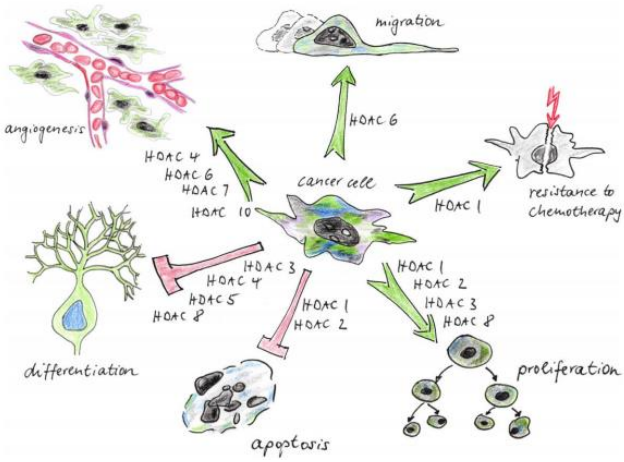
As with many cancers, the gold standard is currently combination chemotherapy involving agents with several different mechanisms of action which increases the chance of success. When diagnosed, patients will undergo a round of chemotherapy that combines four agents (cyclophosphamide, doxorubicin, vincristine & prednisolone – CHOP regimen) aiming at limiting tumor growth and destroying tumor cells. Radiotherapy can also be used to destroy tumors located in the lymph nodes.

Despite these treatments, tumors often recur or do not reduce in size; such tumors are called relapsing and resistant respectively. Other treatments can then be used (such as other chemotherapies, radiotherapy, immunotherapy, etc.) in 2nd line. As of now two products apart from Beleodaq® are authorized in the US in 2nd-line treatment of PTCL (same conditional approval as Beleodaq®): Folotyn® (Pralatexate) and Romidepsine® (Istodax).

The aim of any new treatment is to increase the overall survival while ensuring an acceptable safety profile. In this sense, PTLC is still a disease showing a strong unmet need for improved treatments, alone or in combination.

Belinostat has been approved in the USA for the treatment of PTCL when the 1st line chemotherapy has been ineffective or when the tumor relapses. The safety profile is favorable and it has proven to generate a significant response rates in controlling the growth of the tumors, proving to be an essential option against this severe disease.

HDAC inhibitors: How does Beleodaq® work?



Olaff, Witt et al., Cancer Letters 277 (2009) 8-21

Belinostat is a pan-HDAC inhibitor (HDACi). This means that it inhibits two of the main HDAC families, enzymes involved in multiple mechanisms important for tumor growth. HDACs regulate the function of target genes.

In tumor cells, these HDACs do not function normally, changing the characteristics of the cells so that they multiply in an uncontrolled way leading to tumorisation. The Inhibition of such HDACs aims to prevent the tumor cells from multiplying by inducing cellular death (apoptosis) as well as modulating several other important cellular processes involved in the development of tumors.

BELEODAQ® AND ITS PLAN IN PTCL

BELIEF pivotal Phase IIb study: Positive results leading to FDA approval

This open-label, multi-center, prospective, Phase IIb pivotal trial took place from 2008 to 2010. 129 patients were recruited and treated with belinostat with intravenous infusion, every three weeks. Belinostat proved to have low myelosuppression and even patients with a poor bone marrow reserve tolerated the drug. 26% of patients showed an objective response rate on the tumor. An even higher response rate (45.5%) was observed in patients angioimmunoblastic T-cell lymphoma (AITL), a subtype of PTCL.

After having been granted priority review from the FDA, Beleodaq® received conditional marketing authorization in 2nd-line treatment of peripheral T-cell lymphoma (PTCL) in July 2014 based on these results of the BELIEF study.

This marketing authorization has generated $43 million in revenue over 2014 in milestone payments from US partner Spectrum Pharmaceuticals, who launched the product commercially in August 2014.

From 2nd-line treatment to 1st-line treatment in PTCL

Thanks to its proven effect on tumors, Beleodaq® could also have the potential to be used as a part of the 1st-line treatment of PTCL. To meet the requirements of the FDA, a Beleodaq® Phase III trial is planned to be initiated in H1 2016 for the same PTCL patients, but in 1st-line treatment (*i.e.* first round of treatment) in combination with CHOP (current standard 1st-line treatment), expanding the indication from 2nd- to 1st-line treatment. In order to start a Phase III (pivotal) study of belinostat, Spectrum Pharmaceuticals, Onxeo's US partner, is conducting a Phase I study with the combined treatment Beleodaq® + CHOP to determine the optimal dose of the combination and its safety profile. Results are expected by Q4 2015, which will allow for the finalization of the Phase III protocol in 1st-line treatment of PTCL.

BELEODAQ® BEYOND PTCL

Beleodaq®: A very potent HDACi

On a molecular basis, belinostat is a very potent inhibitor which exhibits a broad spectrum of anti-tumor activity in many cancer cell lines. In addition, it remains active in cell lines resistant to other chemotherapeutic agents.

An excellent safety profile

Beleodaq® has proven to be well-tolerated in clinical use and has been tested in approximately 1,200 patients in over 30 clinical trials. Its excellent safety profile results from low cardiac toxicity and minimal bone marrow toxicity, two side effects commonly observed in oncology drug candidates.

Potential to be used against several other cancers

As a result of the innovative mode of action Beleodaq® has the potential to be of clinical interest for a broad spectrum of hematological and solid cancers either as monotherapy or in combination. The mechanism of action makes it highly suited to combining with current chemotherapeutic agents as well as some of the new generation « immuno-modulating » anticancer treatments. Onxeo is currently building a development plan to assess the product's best future path based notably on the data issued from many studies and trials performed along the Beleodaq® development plan.

Beleodaq® has been subject to several clinical trials and non-clinical studies

In 2014 and 2015, more than 13 clinical publications covered belinostat in the treatment of PTCL, while 6 have been published on other pathologies like carcinoma, advanced myeloid neoplasia, thymic epithelial tumors, or acute myeloid leukemia. Belinostat has also been reported in almost a dozen non-clinical publications covering the field of HDAC inhibitors. Some of these publications are listed below.

- J Clin Oncol. 2015 Aug 10;33(23):2492-9. doi: 10.1200/JCO.2014.59.2782. Epub 2015 Jun 22. **Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study.** O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, Hess G, Jurczak W, Knoblauch P, Chawla S, Bhat G, Choi MR, Walewski J, Savage K, Foss F, Allen LF, Shustov A.
- Future Oncol. 2015;11(11):1659-64. doi: 10.2217/fon.15.62. **Belinostat for the treatment of relapsed or refractory peripheral T-cell lymphoma.** Rashidi A, Cashen AF.
- Mini Rev Med Chem. 2015;15(9):731-50. **Histone deacetylase inhibitors: a review on class-I specific inhibition.** Behera J, Jayprakash V, Sinha BN.
- Cancer Treat Rev. 2014 Oct;40(9):1080-8. doi: 10.1016/j.ctrv.2014.08.001. Epub 2014 Aug 24. **Therapeutic options in relapsed or refractory peripheral T-cell lymphoma.** Coiffier B, Federico M, Caballero D, Dearden C, Morschhauser F, Jäger U, Trümper L, Zucca E, Gomes da Silva M, Pettengell R, Weidmann E, d'Amore F, Tilly H, Zinzani PL
- Cancer Manag Res. 2015 Jun 3;7:145-51. doi: 10.2147/CMAR.S85351. eCollection 2015. **New developments in the treatment of peripheral T-cell lymphoma - role of Belinostat.** Reimer P.
- Arch Pharm Res. 2015 Jun;38(6):933-49. doi: 10.1007/s12272-015-0571-1. Epub 2015 Feb 5. **Histone deacetylase inhibitors in hematological malignancies and solid tumors.** Chun P.

BELEODAQ®: A POTENT AND ATTRACTIVE DRUG

3 questions for Karsten WITT, MD

Karsten WITT is an independent medical consultant, former member of Topotarget's board and former chairman of Topotarget's scientific subcommittee.

Why are HDAC inhibitors such as belinostat of scientific interest?

HDAC (histone deacetylase) is an enzyme family that is key in the regulation of genetic expression and transcription. In cancer cells, HDACs tend to be over-expressed, leading to the growing and multiplying of the tumor cells. Inhibiting HDACs stops the cellular cycle and can cause the death of tumor cells (a process called apoptosis). HDAC inhibitor action can limit the growth of the tumor by turning certain tumor genes on or off, or by enhancing the anti-tumor immune response.

Why is belinostat different from other HDAC inhibitors?

Belinostat stands apart from other already approved HDAC inhibitors as it more potently targets class 1 and 2 HDACs (4 HDAC classes have been identified so far). This compound can thus theoretically have a broader utility as it blocks several additional enzymes. It is then very different from targeted therapies that are specific to one tumor mutation, for example. Belinostat has already been tested in about 1,200 patients, in several clinical studies against a range of cancers (hematologic and solid tumors). We have reason to think that belinostat could work in the treatment of other blood cancers, but also in solid tumors such as liver, bladder, or lung cancer.

What are belinostat's competitive advantages?

Belinostat has been tested both as monotherapy and in combination with a number of standard anti-neoplastic therapies. Pre-clinically, it has been shown to provide additive and synergistic effects when used in combination. Thanks to its specific mode of action, this drug does not overlap with chemotherapies' effects for example. Also, belinostat has a very good safety and tolerability profile. As a monotherapy, it has predictable and manageable side effects. It has also been well-tolerated at full doses in patients when administered in combination with many standard cancer therapies.

Indeed, patients with PTCL often have very low platelet levels, which make many chemotherapies unsuitable because they tend to reduce the level of blood cells further. Thanks to its good safety profile, belinostat can be used in such patients as it has a very low impact on platelet count.

NEWS FROM PARIS ANALYST MEETING

Key figures of H1 2015

Click here to download the corporate presentation

€42.9M
Cash position
at June 30, 2015

€1.53M
Consolidated revenues
in H1 2015

€7.8M
In R&D investment
in H1 2015

50%
of patients randomized
Livatag® Ph III trial in HCC

357
Patents and patent applications
at June 30, 2015

Q&A session

Can you comment on the cash burn rate?

During the first semester, Onxeo's cash burn was €14.3 million, most of it being dedicated to our R&D programs and notably Livatag®. This is in line with our financial plan. Our cash balance of €42.9 million as of June 30, 2015 gives us a visibility until early 2017, taking into account the pursued development of our 3 orphan oncology programs. The cash burn over H2 should be reduced thanks to the repayment of the 2014 R&D tax credit amounting to €2.5 million.

Some people say doxorubicin is old-fashioned and toxic. As it is the core of Livatag®, do you not see a risk?

Not at all! Doxorubicin was developed in the 1970s and has a long track-record of efficacy. It remains one of the gold standards of cancer treatments. It is a very potent drug that kills tumor cells. In Livatag®, doxorubicin has been reformulated with nanoparticles to overcome resistance mechanisms, thus allowing the active drug to reach the nucleus, its site of action. This is the application of a highly innovative technology to a fully recognized active chemotherapy for a new indication, where resistance prevents the original from being effective. The high interest in doxorubicin is also evident from the numerous biotech and pharma companies currently working on new innovative formulations, with the exact same goal: To get the best from this gold standard therapy.

Q&A session (continued)

What about the ReLive study timelines? Can you do 50% recruitment in 1 year?

Recruitment is progressing at a good pace, and in an exponential way as we are opening four additional countries. The study has reached 50% of randomized patients and is currently active in 11 countries. Indeed the plan is to recruit 400 patients but it is an « event-driven » study, event being the death of the patient. First results will be calculated when 285 events have occurred. 400 patients is the number of patients as per statistical calculation needed to reach the 285 events. The preliminary results are expected in early 2017.

What is meant by "preparing" the Phase III study for Validive®?

Phase II results have confirmed the safety profile and the efficacy of Validive®. The Phase III study is expected to start in the first semester of next year. We are currently working on the final definition of the protocol for the study. This is a complex process as it involves experts in oral mucositis, investigators, and also health authorities. Meanwhile, preparation also includes producing the clinical batches of the product that will be used in the study. Finally, preparation consists of selecting clinical centers at the international level that will participate in the study and putting contracts in place with each of them.

LATEST NEWS

Onxeo files application for key Livatag® patent

Livatag® is currently protected by two robust patent families, one of which covers the first generation of nanoparticles of doxorubicin until 2019, with the second covering the specific administration scheme until 2031/2032, depending on the territories.
The new patent application will, if granted, protect the product itself, which is the strongest IP protection. It is based on a specific composition of Transdrug™ nanoparticles that significantly improves the control over the size of these nanoparticles in the synthesis process, thus giving them their unique properties.

The new patent application has been filed in the USA and Europe and will be expanded to include other regions under the patent review procedure.

This is major news for Onxeo's main asset Livatag® as this new patent, if granted, would expand the exclusivity of Livatag on all key markets until 2036, including China which accounts for 50% of HCC patients. This would enable Onxeo to realize the full potential of the product.

NEW ANALYST COVERAGE

Download Full Report

Dr Philippa Gardner from EDISON published on September 8, 2015:
"The next major value inflection point for Onxeo will likely be availability of Phase III Livatag® data for second-line liver cancer expected H117. Prior to Livatag® data, progression with Beleodaq® and Validive® is expected, with the start of further Phase III trials anticipated in H116. Our valuation, which is largely unchanged at €328m, suggests the current share price is ascribing limited value to these assets."

ONXEO – LATEST INTERVIEWS

Dr. Giralt discussing Validive® Phase 2 results at ASCO 2015 on OncLive

Click here to view the video

Judith Greciet comments on H1 results and achievements on BFM Business (in French)

Click here to view the video

CHECK ON OUR WEBSITE FOR MORE INTERVIEWS AND OTHER MEDIA

NEXT EVENTS

LARGE & MID CAP EVENT, PARIS, FRANCE
October 7-8, 2015 – conference dedicated to institutional investors

QUARTERLY INFORMATION AS OF SEPTEMBER 30, 2015
November 5, 2015

ACTIONARIA CONGRESS FOR RETAIL SHAREHOLDERS, PARIS, FRANCE
November 20-21, 2015
➔ Agora of Presidents, November 20, 2015 at 2.25 PM
➔ Investor meeting (room 242 A), November, 21, 2015 at 3.00 PM

ONXEO is listed on Euronext Paris & Nasdaq Copenhagen (ISIN FR0010095596 – ticker ONXEO)