Paris, 09 April 2015, 6pm

Masitinib Treatment of Advanced Pancreatic Cancer

Publication of Phase III Results in Annals of Oncology

Identification of Pharmacogenomic and Clinical Markers Predictive of Masitinib Efficacy in Subgroups

AB Science SA (NYSE Euronext - FR0010557264 - AB), a pharmaceutical company specializing in the research, development and commercialization of protein kinase inhibitors (PKIs), announces the publication of results from the first randomized phase 3 study of masitinib in treatment of advanced pancreatic ductal adenocarcinoma (PDAC). Entitled, '*A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer*' this article and its accompanying Online Supplementary Material are freely accessible online from the peer-reviewed journal Annals of Oncology: http://annonc.oxfordjournals.org/lookup/doi/10.1093/annonc/mdv133. A phase 3 confirmatory study is currently ongoing.

- **Findings revealed that the markers of acyl-CoA oxidase-1 (ACOX1) expression in blood and baseline pain intensity may have prognostic value, with patients from these subgroups experiencing aggressive disease progression while receiving Gemzar® (gemcitabine, from Eli Lilly and Company).**

- **In patients with over-expression of ACOX1 in blood, administration of masitinib in combination with Gemzar® produced a statistically significant overall survival advantage of +6.1 months (Hazard Ratio=0.23[0.10;0.51]) when compared with placebo administered in combination with Gemzar®.**

- **In the pain subgroup, administration of masitinib in combination with Gemzar® produced a statistically significant overall survival advantage of +2.6 months (Hazard Ratio=0.62[0.43;0.89]) when compared with placebo administered in combination with Gemzar®.**

- **Safety of the combination remained acceptable with no overall detrimental effect on quality of life.**

- **A new confirmatory phase 3 trial of masitinib in advanced pancreatic cancer has been initiated, with an objective to replicate these promising results in a prospective manner.**

➢ **Predictive markers of masitinib efficacy**

Reported in this article are results of a phase 3 study conducted by Professor Gaël Deplanque (Saint Joseph Hospital, Paris, France) and colleagues from 73 active centers located predominantly in France, United States and Czech Republic. In this study, 353 patients with inoperable, chemotherapy-naïve, PDAC received gemcitabine in combination with either masitinib or placebo until progression. The primary endpoint was overall survival (OS).

Secondary OS analyses aimed to characterize subgroups with poor survival while receiving single-agent gemcitabine with subsequent evaluation of whether masitinib generated therapeutic benefit in these subgroups.

While median OS was similar between treatment-arms for the overall population, secondary analyses identified two subgroups having significantly poor survival when receiving single-agent gemcitabine. One subgroup was defined by an over-expression of acyl-CoA oxidase-1 (ACOX1) in blood, and the other subgroup was defined by patients exceeding a pain intensity threshold assessed via a visual analog scale (VAS) at baseline. These subgroups represent a critical unmet medical need as evidenced from a shorter median OS of approximately 5.5 months, and comprise an estimated 63% of PDAC patients.

In these subgroups, a significant treatment effect was observed for masitinib with median OS of 11.7 months in the 'ACOX1' subgroup (HR=0.23[0.10;0.51],*P*=0.001), and 8.0 months in the 'pain' subgroup (HR=0.62[0.43;0.89],P=0.012). Despite increased toxicity of the combination compared with single-agent gemcitabine, side-effects remained manageable.

- **Patients with pain**

There is evidence from the scientific literature in support of biological plausibility for the observed masitinib treatment-effect in patients with baseline pain (VAS ≥ 20). The presence of pain in PDAC is thought to flag an increased mast cell activity within the tumor microenvironment which promotes disease progression. Masitinib's highly selective inhibition of mast cell activation is expected to be of therapeutic benefit by impacting on mast cell related remodeling of the tumor microenvironment.

- **Patients with ACOX1 over-expression**

There is evidence from the scientific literature in support of biological plausibility for the observed masitinib treatment-effect in patients ACOX1 over-expression in blood samples. It is thought that ACOX1 over-expression in blood samples from PDAC patients may flag a predominance of pro-tumoral macrophages in the tumor microenvironment. Masitinib induces a accumulation of anti-tumoral macrophages in the tumor microenvironment, thereby counteracting tumor-promoting signals and effectively acting as an immune therapy.

Discovery of this biomarker has also instigated development of a companion diagnostic test associated with masitinib. The test developed by AB Science in collaboration with Acobiom, a biotechnology company specialized in the discovery of new biomarkers and the development of innovative diagnostics focused on personalized medicine, will identify patients most likely to benefit from masitinib treatment. The markers identified in this phase 3 clinical trial are the joint property of AB Science and Acobiom, for which patent protection has been filed. AB Science retains 100% of the rights related to masitinib.

- **Comment**

"A potential unmet medical need among pancreatic ductal adenocarcinoma patients receiving single-agent gemcitabine has been highlighted with the biomarkers of ACOX1 expression in blood and baseline pain intensity demonstrating prognostic value" said Dr Gaël Deplanque of Saint Joseph Hospital, Paris, France, and the principal investigator of this study. *"Moreover, both biomarkers suggested predictive value with the combination of masitinib and gemcitabine appearing to exhibit a positive benefit-risk ratio for the treatment of these subpopulations. A new international phase 3 randomized clinical trial is currently recruiting patients in this indication to confirm these encouraging results, which if successful would support the use of masitinib plus gemcitabine as a new treatment option for these two subgroups pancreatic cancer patients."*

"Pancreatic ductal adenocarcinoma is a heterogeneous disease making it very challenging to treat and which probably explains why survival rates have remained stubbornly poor for so many years. Indeed, such heterogeneity most likely requires targeted-therapy approaches to improve survival in subgroups of the overall population" said Professor Olivier Hermine, President of the Scientific Committee of AB Science. *"Findings from this phase 3 study are consistent with evidence that heterogeneity in tumor biology and microenvironment may be an important determinant of aggressive versus relatively slow disease progression, which in turn leads to variability in terms of treatment susceptibility. It is thought that the presence of baseline pain or an overexpression of ACOX1 effectively identifies those patients with a pro-tumoral immune response. The observed treatment-effect of masitinib are possibly due to its ability to act as an immune therapy, the benefit of which is to extend survival by controlling the aggressiveness, transformation and dissemination of the tumors."*

About masitinib
Masitinib has received orphan drug designation in the treatment of pancreatic cancer from both FDA and EMA.

Masitinib is a new orally administered tyrosine kinase inhibitor that targets mast cells and macrophages, important cells for immunity, through inhibiting a limited number of kinases. Based on its unique mechanism of action, masitinib can be developed in a large number of conditions in oncology, in inflammatory diseases, and in certain diseases of the central nervous system. In oncology due to its immunotherapy effect, masitinib can have an effect on survival, alone or in combination with chemotherapy. Through its activity on mast cells and consequently the inhibition of the activation of the inflammatory process, masitinib can have an effect on the symptoms associated with some inflammatory and central nervous system diseases and the degeneration of these diseases.

About pancreatic ductal adenocarcinoma
Incidence of pancreatic cancer has markedly increased over the last few decades. Pancreatic cancer is now the twelfth most common cancer in the world, with 338,000 new cases diagnosed in 2012[1]. The estimated 5-year prevalence of people in the world living with pancreatic cancer is 4.1 per 100,000. This cancer is almost always fatal, and is the seventh most common cause of death from cancer. Patients diagnosed with pancreatic cancer often have a poorer prognosis compared with other cancers in part because early detection is difficult. At the time of diagnosis, most patients with pancreatic ductal adenocarcinoma present with locally advanced or metastatic disease and only 10-20% of cases are candidates for curative surgery. For over a decade single-agent gemcitabine has been the standard first-line treatment for unresectable, locally advanced or metastatic pancreatic ductal adenocarcinoma. Median overall survival is between 6 to 7 months and 1-year survival rates range between 17 to 25% [2, 3].

[1] http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed 03 March 2015.
[2] Heinemann V, et al. BMC Cancer. 2008;8:82.
[3] Von Hoff DD, et al. N Engl J Med. Oct 31 2013;369(18):1691-1703.

About AB Science
Founded in 2001, AB Science is a pharmaceutical company specializing in the research, development and commercialization of protein kinase inhibitors (PKIs), a class of targeted proteins whose action are key in signaling pathways within cells. Our programs target only diseases with high unmet medical needs, often lethal with short term survival or rare or refractory to previous line of treatment in cancers, inflammatory diseases, and central nervous system diseases, both in humans and animal health. AB Science has developed a proprietary portfolio of molecules and the Company's lead compound, masitinib, has already been registered for veterinary medicine in Europe and in the USA. The company is currently pursuing thirteen phase 3 studies in human medicine in first-line and second-line GIST, metastatic melanoma expressing JM mutation of c-Kit, multiple myeloma, metastatic colorectal cancer, metastatic prostate cancer, pancreatic cancer, mastocytosis, severe persistent asthma, rheumatoid arthritis, Alzheimer's disease, progressive forms of multiple sclerosis, and Amyotrophic Lateral Sclerosis. The company is headquartered in Paris, France, and listed on Euronext Paris (ticker: AB).

Further information is available on AB Science website: www.ab-science.com.

This document contains prospective information. No guarantee can be given as for the realization of these forecasts, which are subject to those risks described in documents deposited by the Company to the Authority of the financial markets, including trends of the economic conjuncture, the financial markets and the markets on which AB Science is present.

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