



Contacts:

Sanofi -aventis
Anne Bancillon
+ 33 (0)6 70 93 75 28

CIRG
Emmanuelle Mékercke
+ 33 (0) 1 58 10 08 97

TAXOTERE[®]-BASED REGIMENS WITH HERCEPTIN[®] IN WOMEN WITH EARLY-STAGE HER2-POSITIVE BREAST CANCER DEMONSTRATE THE HIGHEST REDUCTION IN THE RISK OF DEATH TO DATE AND PROVIDE A TREATMENT OPTION WITHOUT ANTHRACYCLINES

Results of Second Planned Interim Analysis of Phase III Study: BCIRG 006

Paris, France and San Antonio, USA, December 14, 2006 - The Cancer International Research Group (CIRG) and sanofi-aventis Group today announced the results from the second interim efficacy and safety analysis from the BCIRG 006 Phase III breast cancer study, which confirms, at a 3-year median follow-up, that Herceptin[®] combined with Taxotere[®]-based regimens significantly improved disease-free survival for women with early HER2-positive breast cancer.

The BCIRG 006 study randomized patients to receive the control arm AC-T [4 cycles of doxorubicin (A) and cyclophosphamide (C) followed by 4 cycles of Taxotere[®] (T)], or either of two experimental Herceptin[®]- (H) and Taxotere[®]- based therapies: AC-TH (adds 1 year of Herceptin[®] to the AC-T regimen with Herceptin[®] starting concurrently with Taxotere[®]), or TCH (6 cycles of Taxotere[®] and carboplatin (C) with 1 year of Herceptin[®] starting at the first cycle). Patients were prospectively stratified according to their nodal status and hormone receptor status.

The primary endpoint was disease-free survival (DFS). Secondary endpoints included overall survival (OS), safety, including cardiotoxicity, and pathologic and molecular markers. The safety analysis was performed by an Independent Data Monitoring Committee.

The relative reduction in the risk of death was 41% ($p < 0.0041$) and 34% ($p < 0.017$) in the AC-TH and TCH arms, respectively when compared with the non-Herceptin-containing control arm. The relative reduction in the risk of relapse was 39% ($p < 0.001$) and 33% ($p = 0.0003$) for AC-TH and TCH respectively vs. control.

These numbers compare favourably with the relative risk reduction of death of 33% in the American Joint analysis of NSABP B31 and NCCTG N9831 (ASCO 2005) that led to the registration of Herceptin[®] combined with paclitaxel.

This interim analysis showed that 92% and 91% of patients were alive at 4 years in the Herceptin-containing arms (AC-TH and TCH) respectively compared to 86% in the AC-T arm. Of note, TCH (combination of Taxotere[®]/carboplatin/Herceptin[®]), the regimen without

anthracycline, demonstrated similarly significant improvement in disease free and overall survival as the AC-TH arm. However, the TCH arm yielded a five-fold decrease in significant cardiotoxicity when compared to the anthracycline/Herceptin[®]-containing arm.

These data were presented at the 29th annual San Antonio Breast Cancer Symposium (SABCS) in San Antonio, TX – USA.

“These data are outstanding, and because of the way the study was conducted, provide a very accurate picture of the benefits and risks of taxane - Herceptin[®] combinations” said P^r Miguel Martin, Professor of Medical Oncology at the Madrid University, Spain; Head of the Breast Cancer Unit at the University Hospital San Carlo, Madrid; Chairman of the Spanish Group on Breast Cancer Investigations (GEICAM) and an Investigator in the BCIRG 006 study.

“This trial demonstrates an optimal therapeutic index for these patients with the use of TCH (which did not include doxorubicin), thus avoiding the significant cardiac damage related to the sequential use of anthracyclines and Herceptin[®]” said Dennis Slamon, PhD, MD, Co-Chair of the BCIRG 006 study and Director of Clinical and Translational Research at UCLA's Jonsson Comprehensive Cancer Center. *“In this interim analysis, 6 cycles of chemotherapy in the TCH regimen provided similar benefit as AC-TH (8 cycles of chemotherapy in total) without increasing cardiotoxicity. In addition, no secondary leukemias have been observed so far in the TCH arm compared to four leukemia events in the anthracycline-containing arms, although further long term hematologic adverse event follow up will continue. These data should help influence daily practice with TCH being considered an option for women with early stage HER2 positive breast cancer, irrespective of nodal status”.*

The cardiac toxicity of the 2 experimental arms significantly favored the TCH regimen. No cardiac deaths were observed in either arm. There were 20 congestive heart failure events in AC-TH versus four in the TCH arm. Moreover, there were 50% fewer asymptomatic declines in cardiac function in the TCH arm as compared to AC-TH.

Also, in terms of other toxicities, the TCH arm was better to AC-TH with regards to a number of parameters including sensory and motor neuropathies (36.1% vs 49.7% and 4.2% vs 6.3% respectively), nail changes (28.7% vs 43.6%), and myalgia (38.6% vs 52.8%). However, more grade 3 and 4 thrombocytopenia (5.4% vs 1.2%) and anemia (5.8% vs 3.1%), were observed in the TCH arm compared to the AC-TH arm.

About the BCIRG 006 Study

The BCIRG 006 study was designed to maximize efficacy while minimizing toxicity in adjuvant Herceptin[®]-based therapies. Between April 2001 and March 2004, the study enrolled 3, 222 women with early stage HER2-positive breast cancer, with positive axillary lymph nodes (LN) as well as those without LN involvement. BCIRG continues to closely monitor patients for long-term efficacy and safety analyses.

In this second interim analysis, at a 3-year median follow-up, AC-TH and TCH significantly improved DFS and OS as compared to the control arm.

The relative reduction in the risk of relapse was 39% ($p < 0.001$) and 33% ($p = 0.0003$) respectively, for AC-TH and TCH vs control.

The relative reduction in the risk of death was 41% ($p < 0.0041$) and 34% ($p < 0.017$) respectively, for AC-TH and TCH vs control.

In addition, the absolute DFS benefit at 4 years is similar for the two Herceptin[®]-containing arms (6% and 5% for AC-TH and TCH, respectively). Notably, the same level of DFS and OS benefit was also obtained for the 29% of node negative patients enrolled in the study.

In terms of safety, there was a significant difference in the major toxicity that has been consistently seen with Herceptin[®]-based therapies ie cardiac toxicity. Common to all of the Herceptin[®] adjuvant trials was the evaluation of congestive heart failure and cardiac-related deaths. As mentioned above, the cardiac toxicity of the 2 experimental arms significantly favored the TCH regimen. Further, in terms of other toxicities, the TCH regimen appeared to also be more favourable than the AC-TH regimen

The BCIRG investigators and leadership wish to express their deep appreciation to the women who willingly participated in this randomized controlled trial and their commitment to improving outcomes for all women challenged with breast cancer. Slamon noted that *“they are our colleagues in this study rather than the research subjects.”*

The study was sponsored by sanofi-aventis, had financial support from Genentech, and was conducted by CIRG.

About Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women. It is the second-leading cause of cancer death in women after lung cancer, and since 1990 is increasing predominantly in women 50 and over. It is the first cause of cancer mortality in women of 40 to 59 years old. According to the American Cancer Society, an estimated 211,240 women will be diagnosed with breast cancer and approximately 40,000 women will die of the disease in the United States in 2005. A woman is diagnosed with breast cancer in the United States every three minutes. The risk of a woman developing breast cancer during her lifetime is approximately 13 percent (about one in seven of all women in the United States). In the European Union, more than 191,000 new cases are diagnosed each year and more than 60,000 women will die. Of women with breast cancer, 20 to 25% of these women will have HER2 positive breast cancers. With earlier screening and diagnosis, early management of patients may offer better chances of survival.

About Taxotere[®]

Taxotere[®] is currently approved in 5 different cancer types :

• In Breast Cancer

In the United States and in Europe Taxotere[®], is approved to treat patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. It is also approved in Europe in combination with doxorubicin for patients who have received prior cytotoxic therapy for this condition and in combination with capecitabine after failure of cytotoxic therapy which would have included anthracycline. In the adjuvant setting (post surgery) it is approved in the US and in Europe in combination with doxorubicin and cyclophosphamide (TAC regimen) for the treatment of patients with operable, node-positive breast cancer. Finally, in Europe, Taxotere[®] is approved in combination with trastuzumab for the treatment of patients with metastatic breast cancer- overexpressing HER2 receptor.

• In Lung Cancer

In the US and in Europe Taxotere[®], in combination with cisplatin, is approved for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not received prior chemotherapy, and it also is approved, as a

single agent, for patients with unresectable locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy.

• **In Prostate cancer**

Taxotere[®] is approved for use in combination with prednisone as a treatment for androgen-independent (hormone-refractory) metastatic prostate cancer in the US and in Europe.

• **In Gastric (Stomach) cancer**

The FDA and the Committee for Medicinal Products for Human Use (CHMP) of the European Agency for the Evaluation of Medicinal Products (EMA) approved in March 2006, the use of Taxotere[®] Injection Concentrate in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced stomach (gastric) cancer, including cancer of the gastro oesophageal (GE) junction, who have not received prior chemotherapy for advanced disease.

• **In Head and Neck Cancer**

In October 2006, the European Medicines Agency (EMA) and the FDA approved Taxotere[®] (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN).

About CIRG:

BCIRG is the breast cancer division of the Cancer International Research Group (CIRG). CIRG has performed a number of new and innovative clinical trials with new cancer therapies. Active participation by its global network of dedicated cancer research leaders and investigators has made CIRG the success it is today. The organization is dedicated to bringing rational and innovative therapeutic concepts into the clinical trial setting through translational approaches based on the underlying biology of the disease. To further this objective, CIRG recently merged with Translational Oncology Research International (TORI). TORI is a smaller clinical trials group directly linked to several basic research laboratories in which new therapeutic molecules are evaluated.

CIRG has offices located in Paris (France) and Edmonton Alberta (Canada). For information about CIRG, please visit our website: www.cirg.org.

About sanofi -aventis

Sanofi-aventis is the world's third largest pharmaceutical company, ranking number one in Europe. Backed by a world-class R&D organisation, sanofi-aventis is developing leading positions in seven major therapeutic areas: cardiovascular, thrombosis, oncology, metabolic diseases, central nervous system, internal medicine and vaccines. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).