

## Isis Pharmaceuticals and Eli Lilly and Company Announce Results of Affinitak(TM) Phase III Clinical Trial in Non-Small Cell Lung Cancer

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CARLSBAD, Calif. and INDIANAPOLIS, March 17 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) and Eli Lilly and Company (NYSE: LLY) announced today results of a Phase III trial that evaluated the antisense agent Affinitak™ when combined with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC).

No difference was observed in a primary log-rank analysis of the overall survival of the two groups ( $p=0.81$ ). Survival was the primary endpoint of the study. Patients receiving Affinitak plus the chemotherapy regimen of carboplatin and paclitaxel experienced a median survival of 10 months, compared to 9.7 months for patients receiving chemotherapy alone. The median survival of the control group was longer than expected, in light of the fact that 87% of patients had Stage IV disease.

Other key findings from the trial of 616 chemotherapy naive patients with Stage IIIb or Stage IV NSCLC are as follows:

- Using a stratified log-rank statistical analysis that considered predefined variables, including duration of treatment, survival of the Affinitak treated patients was greater than that of the patients in the control arm. Based on all 616 patients in the study, this result was statistically significant ( $p=0.048$ ) and merits further evaluation.
- A survival analysis of the 256 patients who completed the prescribed course of chemotherapy showed a median survival of 17.4 months for Affinitak patients versus 14.3 months for patients receiving chemotherapy alone ( $p=0.054$ ). The prescribed course of therapy was 6 cycles of treatment.
- Additionally, in the 256 patients completing the prescribed course of chemotherapy, results favored the Affinitak group across multiple secondary endpoints.
- Treatment groups in the trial were comparable with regard to all major prognostic factors. For example, each group had approximately 87% of patients with Stage IV disease and was comparable in terms of types of lung cancer.
- Addition of Affinitak to carboplatin and paclitaxel was well tolerated. There were no increases in severe toxicities or toxicity related deaths in patients receiving Affinitak, compared to those receiving chemotherapy alone. The most common side effects among patients in the study were fatigue and nausea. Patients in the study receiving Affinitak in combination with chemotherapy had a higher rate of moderate thrombocytopenia, nausea and vomiting. Further, because Affinitak is given via continuous intravenous infusion, Affinitak treated patients had a higher incidence of catheter-related infections. □

The complete findings of this trial will be submitted for scientific presentation at an appropriate medical meeting later this year.

"The observation that those patients who completed the prescribed course of therapy appeared to survive longer than patients receiving chemotherapy alone merits further evaluation," said Jon Holmlund, M.D., Isis' Vice President, Development.

"The partnership between Lilly and Isis and our commitment to further investigate the antisense platform in cancer is unchanged," said Paolo Paoletti, M.D., Vice President of Oncology Products, Eli Lilly and Company. "We expect to continue to study the utility of antisense technology in cancer clinical trials."

"While we are disappointed with the outcome of this trial, we plan to work closely with our partner, Lilly, to determine the future of this drug in non-small cell lung cancer," said Stanley Crooke, M.D., Ph.D., Isis' Chairman and CEO.

Isis and Lilly will conduct a live webcast conference call to review the Affinitak Phase III trial results on Monday, March 17 at 9:00 AM Eastern time. To participate over the Internet go to [www.isispharm.com](http://www.isispharm.com) or <http://www.firstcallevents.com/service/ajwz376907279gf12.html>. A replay of the webcast will be available at this address for up to 30 days.

#### About Affinitak

In the field of oncology, antisense drugs are designed to shut down the production of proteins associated with cancer. Specifically, Affinitak selectively inhibits the production of protein kinase C-alpha, which has been implicated in tumor growth and maintenance. By targeting cells expressing abnormal levels of PKC-alpha Affinitak may have therapeutic potential in a wide array of common cancers (for more on PKC-alpha visit [www.pkc-alpha.com](http://www.pkc-alpha.com) ).

#### About NSCLC

In the U.S., according to the American Cancer Society, approximately 171,000 new cases of lung cancer will be diagnosed and more than 157,000 Americans will die due to the disease in 2003. Lung cancer is the leading cause of cancer death for men and women. More people die of lung cancer than of colon, breast and prostate cancers combined.

Globally non-small-cell lung cancer is the most common type of lung cancer, accounting for almost 80 percent of lung cancers. NSCLC affects more than 1 million men and women worldwide each year and is most often characterized by a poor survival rate.

#### Lilly

Lilly, a leading innovation-driven corporation is developing a growing portfolio of best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers -- through medicines and information -- for some of the world's most urgent medical needs.

#### Isis

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene® (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 antisense products in its development pipeline with two in late-stage development and six in Phase II human clinical trials. Affinitak, an inhibitor of PKC-alpha, is in a Phase III trial for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in a Phase III trial in Crohn's disease. Isis has a broad patent estate as the owner or exclusive licensee of nearly 1,200 issued patents worldwide. Isis' GeneTrove™ division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. Ibis Therapeutics™ is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

This press release contains forward-looking statements concerning the development and therapeutic potential of Affinitak. Any statement describing a goal, expectation, intention or belief of Isis or Lilly is a forward-looking statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and financing such activities. Affinitak has not been proven safe and effective and there are no guarantees that it will receive regulatory approvals or prove to be commercially successful. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Lilly or Isis research and development programs are described in additional detail in Lilly's most recently filed reports on Form 10-K and 10-Q or Isis' Annual Report on Form 10-K and quarterly reports on Form 10-Q for the periods ended December 31, 2001 and September 30, 2002 respectively. These forms are on file with the U.S. Securities and Exchange Commission, copies of which are available from both companies. Lilly and Isis undertake no duty to update forward-looking statements.

SOURCE Isis Pharmaceuticals, Inc.; Eli Lilly and Company