

Limited Press Release

October 2011

Superiority of Lipoplatin to cisplatin in response rate as first-line treatment against non-squamous non-small cell lung cancer (ns-NSCLC) from a randomized Phase III study

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Dr. George Stathopoulos and his collaborators announced exciting data from a randomized Phase III study against non-squamous non-small cell lung cancer (ns-NSCLC) mainly representing adenocarcinomas of the lung using Lipoplatin™. The results of this trial were published in October 2011 in *Cancer Chemother Pharmacol.* Vol 68, pages 945-950 (Open access at <http://www.springerlink.com/content/c2624362664404t5/>). This study used Lipoplatin in combination with paclitaxel as first line treatment against ns-NSCLC and compared response rates and toxicities to a similar group of patients treated with cisplatin plus paclitaxel. This study has demonstrated an increase in tumor response rate in the Lipoplatin arm (59.22% of patients) versus the cisplatin arm (42.42%, of patients) which was statistically significant (p value = 0.036). Most major toxicities of cisplatin, especially nephrotoxicity were also reduced in the group of patients treated with Lipoplatin.

Lipoplatin™ is a liposomally encapsulated cisplatin formulated by Regulon, that has undergone extensive clinical testing since 2001. The introduction of cisplatin in 70s has revolutionized cancer chemotherapy, especially of epithelial malignancies, most notably, testicular cancer. Carcinomas of the head and neck, bladder, ovaries, testis, esophagus, and lung are the most common malignancies that are sensitive to cisplatin when combined with a second or third cytotoxic agent. Attempts to develop platinum compounds to reduce the side effects of cisplatin have resulted in the introduction of carboplatin and oxaliplatin. However, both of these drugs have proven to have inferior response rates to cisplatin especially in lung cancer. Other cytotoxic agents such as taxanes (paclitaxel, docetaxel), gemcitabine, vinorelbine, pemetrexed, and irinotecan have also been used as substitutes of cisplatin; however, none of these agents has demonstrated superior efficacy to cisplatin in lung cancer. This study represents the first time a drug has improved on

cisplatin's response rate in non-squamous NSCLC.

Median survival times were 10 months for the Lipoplatin arm and 8 months for the cisplatin arm, with a p-value of 0.155. The median duration of response was 7 months for the Lipoplatin arm and 6 months for the cisplatin arm. Although not statistically significant, these results suggest the potential for superior overall survival (OS) for Lipoplatin compared to cisplatin, a hypothesis that will be tested in a larger trial. Furthermore, among the responders to Lipoplatin a subgroup of patients demonstrated a substantially higher overall survival than a comparable subgroup of cisplatin responders. After 10 months, 30% of patients in the Lipoplatin arm, as compared with just 16% of patients in the cisplatin arm, were without disease progression. By the end of the trial, there were 32 patients alive, 21 from the Lipoplatin arm (20.39%) and 11 from the cisplatin arm (11.11%). Thus, after 18 months, the number of surviving patients was approximately double for Lipoplatin versus cisplatin.

The clinical development of Lipoplatin in adenocarcinomas establishes this drug as the most active platinum drug with significantly lower side effects.

Regulon has obtained the consent of EMA for a registrational Phase III study (~880 patients) with a Lipoplatin plus Alimta vs Cisplatin plus Alimta as first-line treatment of non-squamous NSCLC. This study is expected to commence in over 50 oncology centers across 10 EU countries, as well as including patients from the USA and Asia.

"These are exciting data that open new avenues in molecular medicine and in the treatment of NSCLC" said Teni Boulikas, Ph.D., President and CEO of Regulon. Dr. Boulikas added, "seldom does a new drug go first-line against cancer, usually it gains initial approval as a second- or third-line treatment. But given the strong data achieved thus far, in terms of both efficacy and safety, Lipoplatin aspires to be approved as first-line treatment against the world's largest cancer indication, non-squamous NSCLC".

About Regulon

Regulon Inc. is a private biopharmaceutical company based in Silicon Valley, committed to the discovery and development of nanopharmaceuticals in oncology. Currently these are based on liposomal formulations of off-patent

platinum drugs (cisplatin and oxaliplatin) generating new branded names. The technology is also applicable to numerous other anticancer drugs reducing toxicity and achieving passive tumor targeting. Regulon's technology platform is protected by a broad array of issued and applied patents.

<http://regulon.org/>

About Lipoplatin

Regulon's lead product Lipoplatin™, is a liposomally encapsulated cisplatin. It has completed successfully its Phase III clinical evaluation. Only one in 1,000 drugs tested by Pharma and Biotech Companies gets past Phase III successfully.

Lipoplatin seems to be solving three major and outstanding problems in clinical oncology:

- 1. Tumor targeting** of the drug regardless of the type of tumor or its size. Indeed, Regulon's nanoparticles can target the primary tumor and its metastases. Over 95% of cancer patients succumb from complications from metastases. Usually there are micrometastases of a size of a pinhead that are invisible by CT scans , x-rays or other conventional imaging technologies. These micrometastases need to sprout blood vessels for their growth and thus, Lipoplatin nanoparticles can detect, target and cause their destruction in addition to the destruction of the primary tumor.
- 2. Crossing of the cell membrane barrier** by Lipoplatin nanoparticles leading to delivery of their toxic payload inside the cytoplasm of the tumor cell where it is needed for anticancer efficacy
- 3. Lowering of the side effects** of the classical chemotherapy. Because of the lipid shell, Lipoplatin does not harm the cells of the kidney and other normal tissues to cause nephrotoxicity and other side effects. On the contrary, because of its extravasation in tumors (especially those with high vascularization as the nonsquamous NSCLC, gastric and breast cancers) and its penetration inside the cell and because of its lipid shell promotes phagocytosis by tumor cells.

Lipoplatin's safety has been documented in over 600 patients treated with this product.

Lipoplatin has significant pharmaco-economic benefits: (i) it is being administered on an outpatient basis and without pre- or post-hydration compared to cisplatin treatment that requires 2 days of hospitalization. (ii), there is less use of

antiemetics and of the expensive hemotopoietic factors EPO and G-CSF with Lipoplatin, compared to cisplatin, treatment. (iii) The absence of Grade III-IV nephrotoxicity in Lipoplatin also eliminates the expensive hemodialysis treatments for life required for a percentage of patients treated with cisplatin and causing permanent damage to their kidneys. (iv), because of its lower neuropathy and improvement in Quality Of Life (QOL) it remains as the drug of choice. (v) Because of the low cumulative toxicity, Lipoplatin has been administered to over 27 doses to a single patient compared to maximum 6 doses allowed for cisplatin and thus, Lipoplatin has application as a maintenance therapy to extend the life span of cancer patients.