

# Limited Press Release

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**Exciting results from a randomized Phase III study comparing Lipoplatin to cisplatin as first-line treatment against non-small lung cell cancer (NSCLC) and its subgroup of adenocarcinomas**

Regulon, Inc. Mountain View, California and Athens Greece

Final and exciting data from a randomized Phase III data on Lipoplatin™, a liposomally encapsulated cisplatin formulated by Regulon, has been announced in by the Oncology group of Dr. George Stathopoulos and his collaborators at "Annals of Oncology", the official journal of ESMO (European Society of Medical Oncology) (free access at: [Oxford Journals](#)). This non-inferiority study using Lipoplatin as first line treatment against Non-Small Cell Lung Cancer (NSCLC) in combination with paclitaxel compared response rates and toxicities to a similar group of patients treated with cisplatin plus paclitaxel. This study has demonstrated statistically significant reduction of most major toxicities of cisplatin, especially nephrotoxicity, by its replacement with Lipoplatin.

The obtained results are significant for those patients required to have cisplatin-based chemotherapy; cisplatin is being used for a broad range of epithelial malignancies, including those of the lung, ovarian, testicular, urinary bladder and cervical cancers while its off label use is extended to a broad range of additional cancers. Furthermore, cancer patients treated with Lipoplatin have considerably better quality of life compared to classic chemotherapy.

Pre-publication of the Phase III results (on all subtypes of NSCLC) was enthusiastically accepted by the international community of oncologists who have voted this article as number one in oncology (71 stars) in the professional site DocGuide.com screening 2,000 journals with 300,000 subscribers.

<http://beta.docguide.com/liposomal-cisplatin-combined-paclitaxel-versus-cisplatin-and-paclitaxel-non-small-cell-lung-cancer-r>

The response rate was similar across all histological sybtypes in this Phase III study. However, analysis of the adenocarcinoma subtype from the same trial is bringing a revolution in molecular medicine and the way

adenocarcinomas will be treated by oncologists in the future. Indeed, Lipoplatin gave a 59.5% response vs 42.5% with cisplatin (in their combination with paclitaxel) in lung adenocarcinomas (more specifically non-squamous NSCLC) and this difference was statistically significant (p-value = 0.036). The median survival time in months between the two arms was for Arm A (Lipoplatin) 10 months and for Arm B (Cisplatin) 8 months, p-value 0.6822. After 18 months the number of surviving patients was double for Arm A versus Arm B. These results will be published in Q4 2010 by the same group of investigators. The data were reported at the 2010 Annual ASCO (American Society of Clinical Oncology) meeting (Abstract No: 7579) see: [http://abstract.asco.org/AbstView\\_74\\_42160.html](http://abstract.asco.org/AbstView_74_42160.html)

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

Cisplatin administration requires pre- and post-hydration to the patients and their admission to the hospital is done one day before and one day after treatment to avoid kidney toxicity and to control other side effects. On the contrary, Lipoplatin was administered on an outpatient basis without pre- or post-hydration making its use simpler and safer.

Regulon has obtained the consent of EMEA for a registrational Phase III study with a Lipoplatin plus Alimta vs Cisplatin + Alimta on adenocarcinomas of NSCLC. This study is expected to become initiated in over 50 oncology Centers across 10 EU countries.

"These are exciting data and open new avenues in molecular medicine and in the treatment of NSCLC". It is seldom that a Company has chances to see its drug as first-line treatment against cancer, usually a new drug gains approval as second- or third-line-treatment. "Lipoplatin aspires to achieve first line treatment against the world's largest cancer indication, NSCLC" said Teni Boulikas, Ph.D. President and CEO of Regulon.

It is for the first time since 70s a drug shows a significant advantage to cisplatin in spite of efforts that resulted in the synthesis of over 3,000 platinum drugs, testing in clinical studies of 35 of these and marketing authorization of carboplatin and oxaliplatin:

([http://www.cancer-therapy.org/CT/v5/B/PDF/63.\\_Boulikas,\\_537-584.pdf](http://www.cancer-therapy.org/CT/v5/B/PDF/63._Boulikas,_537-584.pdf)). For example carboplatin and oxaliplatin, two world-wide approved platinum drugs, achieved a lowering of some side effects of cisplatin but no superiority. In addition, carboplatin has a higher myelotoxicity than cisplatin and oxaliplatin a higher neurotoxicity compared to cisplatin. The efficacy of carboplatin in lung adenocarcinomas is lower than that of cisplatin as demonstrated from a meta-analysis on ~3,000 patients.

### **About Lipoplatin**

Lipoplatin is based on the world-wide approved and known to all medical professionals cisplatin. Lipoplatin is a liposomally encapsulated form of cisplatin that in previous human studies has shown a 40-fold higher accumulation in solid tumors and metastases after intravenous administration to patients (<http://www.ncbi.nlm.nih.gov/pubmed/16080562>). Lipoplatin is currently under Phase III clinical evaluation against NSCLC in an EMEA registrational study. Lipoplatin is being tested as first line against pancreatic cancer as an add-on to gemcitabine in a different EMEA pivotal study.

Lipoplatin has significant pharmaco-economic benefits since it is being administered on an outpatient basis and without pre- or post-hydration compared to cisplatin treatment that requires 2 days of hospitalization. In addition, there is less use antiemetics and of the expensive hemotopoietic factors EPO and G-CSF with Lipoplatin, compared to cisplatin, treatment. 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.

### **Tumor targeting by Lipoplatin**

The mechanism of tumor targeting by Lipoplatin is based on the property of Regulon's nanoparticles (110 nm in diameter) to find the tumors and metastasis in the body and to concentrate inside them; this process, known as extravasation, takes advantage of the compromised endothelium of the vasculature of the tumors generated during neoangiogenesis. Studies on patients who were infused intravenously Lipoplatin and underwent surgery the following day have shown an accumulation 10-200 times higher in tumor or metastases specimens compared to

platinum levels in specimens from the adjacent normal tissue.

Furthermore, unlike synthetic nanomaterials, lipids that compose the Lipoplatin nanoparticles are natural macromolecules and there are no side effects from the liposome shell to patients. Liposomes are EMEA- and FDA-approved components of branded drugs such as DOXIL/Caelyx.

Recent unpublished studies have shown that entrance of Lipoplatin nanoparticles labeled with fluorescent lipids to cells in culture is extremely rapid with an initial (5 min) localization in the cell membrane, followed by a cytoplasmic perinuclear localization after several hours. Thus Lipoplatin, unlike DOXIL, is able to cross the cell membrane barrier after it reaches tumor tissue.

### **Comparison to other formulations**

Lipoplatin's success in NSCLC is significant considering the poor efficacy data reported for another liposomal cisplatin, known as SPI-77 developed by Sequus/Alza. Indeed, in an article by White and coworkers published at *British Journal of Cancer* (2006) **95**, 822–828 the liposomal cisplatin formulation SPI-77 has shown a mediocre 4.5% efficacy in NSCLC. For the full publication of this Phase II study on SPI-77 in NSCLC see:

<http://www.nature.com/bjc/journal/v95/n7/full/6603345a.html>

A number of other nanotechnology anticancer products are emerging in various research institutions or Biotech and Pharmaceutical Companies; however, most products or formulations are at preclinical or early clinical stage; one out of 1000 of these will reach the market in the next 10 years. An example is a new cisplatin formulation, LiPlaCis; its observed safety profile suggested no benefit over standard cisplatin formulations resulting to the early cessation of its clinical development. For additional information see: <http://www.ncbi.nlm.nih.gov/pubmed/20801016>.

### **About Regulon**

Regulon Inc. is a private biopharmaceutical company committed to the discovery and development of nanopharmaceutics in oncology. Currently these are based on 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/>